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VALUE OF BRONCHOSCOPY IN CLINICAL PRACTICE

A REVIEW OF 1,109 EXAMINATIONS

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Bronchoscopy now has an established place in the investigation of respiratory disease. Its most important application is in the field of lung cancer, in which it often provides conclusive proof of the diagnosis at a much earlier stage than would otherwise be possible. Bronchoscopy may also be of value in the investigation of pulmonary tuberculosis and bronchiectasis, in which abnormalities of the bronchi may alter the course of the disease or modify treatment.

During the past few years there has been a steadily increasing demand for the provision of facilities for bronchoscopic examination. This has been due not only to the increasing prevalence of lung cancer but also to a change in attitude among physicians, who now regard bronchoscopy as an indispensable adjunct to clinical and radiographic examination wherever there is the remotest possibility of a lung tumour being present. Although this attitude is wholly admirable it could perhaps be exploited to even better advantage if current views on the value and limitations of bronchoscopy were more widely known, and this paper is an attempt to present that information in the light of experience with over 1,000 consecutive examinations.

At the respiratory diseases units of two Scottish hospitals, bronchoscopy was carried out on 1,109 patients during the four-year period 1952 to 1956. Of these, 950 were under our direct clinical supervision, and we were able to establish a definite diagnosis in all of them. The remaining 159 patients were referred from other hospitals specifically for bronchoscopy: a diagnosis of tumour was made in 30 and they were transferred to our supervision for their investigation to be completed; the remaining 129 were returned to their own physicians for further investigation once we were satisfied that the presence of a tumour had been excluded on adequate radiographic and bronchoscopic evidence. As full details of the final diagnosis were not always available in these cases they have not been included in the analysis.

Indications for Bronchoscopy.—The 1,109 cases were submitted to bronchoscopy for one of the following reasons: (1) to establish a diagnosis in patients suspected on clinical or radiographic grounds of having a tumour; (2) to exclude the presence of a tumour or any other cause of bronchial obstruction in patients believed to have bronchiectasis; (3) to exclude the presence of a tumour or to confirm a diagnosis of endobronchial tuberculosis in patients known to have pulmonary tuberculosis; and (4) other reasons—for example, removal of foreign bodies or aspiration of obstructing secretions.

Method

Premedication.—All in-patients submitted to bronchoscopy—that is, about two-thirds of all cases—were given a barbiturate to allay apprehension and because such drugs may reduce the incidence of sensitivity reactions to local analgesia with cocaine and its analogues (Penman, 1957). One hour before the examination all patients were given a subcutaneous injection of papaveretum hydrochloride ("omnopon") and hyoscine. The dosage, which was assessed individually according to the patient's height and weight, ranged between ½ and ¾ gr. (22 and 44 mg.) of omnopon and 1/150 and 1/75 gr. (0.43 and 0.87 mg.) of hyoscine. Particular caution was observed in elderly or debilitated patients, who seem abnormally susceptible to morphine and hyoscine in standard dosage, and in those with severe emphysema or bronchial asthma in whom hypoventilation caused by the morphine may lead to anoxia and retention of carbon dioxide. All those patients normally received one-half to two-thirds of the standard dose, but in a few cases with severe emphysema omnopon was omitted altogether and only atropine was given.

Anaesthesia.—Every bronchoscopic examination was carried out under local surface analgesia. In four-fifths of the cases a 1% solution of amethocaine was used, the usual total dose being 6 to 10 ml., to which was added 0.3 to 0.5 ml. of 0.1% adrenaline. In the remainder, 4 to 8 ml. of 4% lignocaine ("xylocaine") was used in place of amethocaine. In all cases the upper limit of dosage was strictly observed.

Technique of Bronchoscopy.—A Negus bronchoscope of appropriate calibre was employed in all cases and full use was made of the direct, right-angle, and retrograde telescopes. An attempt was always made to inspect every segmental orifice normally accessible to bronchoscopic vision, and only very seldom could this not be done. In general, the right-angle telescope was of much

greater value than the retrograde telescope for inspection of the upper lobar bronchi. The same instrument also provided a useful view within the apical (lower) segmental bronchus.

Biopsy was performed in every case which showed a visible bronchial abnormality. If there was presumptive radiographic evidence of a tumour in the apical or basal segments of either lower lobe, in the right middle lobe, in the lingular segment of the left upper lobe, or in the anterior segment of the right upper lobe an attempt was made, even if there was no visible bronchial abnormality, to obtain histological confirmation of the diagnosis by so-called "blind biopsy." This was done by introducing biopsy forceps deeply into the related bronchus and cautiously removing tissue. If the forceps were felt to grip a carina they were withdrawn and reintroduced in a slightly different direction. In some of these cases a fine gum-elastic bougie was inserted into the bronchus of the segment or lobe under suspicion prior to "blind biopsy." Occasionally in the presence of a tumour obstruction of a segmental bronchus was detected in this way and bleeding sometimes followed withdrawal of the bougie. Bronchial aspirate obtained after bouginage was examined histologically in the hope that fragments of malignant tissue might have been dislodged, but in practice this technique proved to be unsuccessful.

Complications

In the total of 1,109 bronchoscopic examinations there were one fatal and three non-fatal complications.

Fatal Complications.—A man aged 66 died 10 hours after bronchoscopy. He had severe emphysema in addition to a bronchogenic carcinoma, and death was due to carbon dioxide narcosis, possibly contributed to by the presence of extensive cerebral metastases. The severity of his emphysema had not been correctly assessed and he was given a standard dose of omnopon and hyoscine. After the bronchoscopy his pulmonary ventilation was depressed and he rapidly became comatose. He died without recovering consciousness despite the administration of N-allylnormorphine, nikethamide, and aminophylline.

Non-fatal Complications.—(*a*) Of local analgesia:—No patient developed symptoms attributable to either of the two local analgesic agents employed. (*b*) Of bronchoscopy itself: A woman aged 63 developed respiratory obstruction from oedema glottidis 14 hours after bronchoscopy and required tracheostomy. She subsequently made a complete recovery. (*c*) Of bronchial biopsy:—Two patients had an abnormal degree of haemorrhage which continued for about half an hour after biopsy, in both instances after tissue had been taken blindly from within a basal bronchus. The airway was maintained by constant aspiration of the blood until the haemorrhage ceased spontaneously.

Pneumothorax and mediastinal emphysema resulting from perforation of the bronchial wall did not occur in this series, but outside the period under review a pneumothorax was recorded twice, each time after "blind" biopsy, and mediastinal emphysema once, after biopsy of a fibrous stenosis of the left lower bronchus. The pneumothorax in both cases was shallow and caused no symptoms. The mediastinal emphysema was accompanied by gross subcutaneous emphysema in the chest, neck, and face, but this subsided completely within a few days.

Based on the final diagnosis, the 980 patients available for detailed analysis can be divided into four groups: (1) bronchogenic carcinoma, 276; (2) bronchiectasis, 118; (3) pulmonary tuberculosis, 132; (4) other conditions, 458.

A dual diagnosis of pulmonary tuberculosis and bronchogenic carcinoma in four cases accounts for the figures totalling 984 instead of 980.

The results of bronchoscopic examination in the first three groups are reviewed in detail, but only a brief account is given of the fourth group, as few of these cases showed any abnormality at bronchoscopy.

Value of Bronchoscopy in Specific Conditions.

1. Bronchogenic Carcinoma

800 patients in whom a bronchogenic carcinoma was suspected were submitted to bronchoscopic examination. The diagnosis was finally established in 276 (34%). Histological evidence of carcinoma was obtained by bronchial biopsy in 168 (61%) of the 276 cases. Bronchoscopic examination was of no diagnostic value in 75 cases (27%), and of only limited value in an additional 33 cases (12%), in which the macroscopic appearances were consistent with tumour but biopsy was negative.

In an attempt to evaluate the factors influencing the results of bronchoscopic examination in patients with bronchogenic carcinoma the macroscopic appearances and the results of bronchial biopsy were analysed in relation to (*a*) the radiographic changes, and (*b*) the occurrence of haemoptysis. Finally, we tried to show how the results of bronchial biopsy were influenced by the macroscopic appearances at bronchoscopy.

Results of Bronchoscopic Examination in Relation to Radiographic Findings

Table I relates the frequency of macroscopic abnormalities at bronchoscopy and the results of bronchial biopsy to the type and situation of the lesion shown on the radiographs. The terms "normal" and "abnormal" in relation to bronchoscopy refer to the macroscopic appearances irrespective of the results of bronchial biopsy, which are shown separately. Radiographic classification is based on the interpretation of postero-anterior and lateral films.

TABLE I.—*Bronchogenic Carcinoma. Analysis of the Results of Bronchoscopic Examination in Relation to the Radiographic Findings*

	Bronchoscopy		Total	Positive Bronchial Biopsy
	Normal	Abnormal		
Type of radiographic abnormality:				
Atelectasis ..	11	82 (88%)	93	77 (83%)
Uniform opacity	17	49 (74%)	66	37 (56%)
Patchy opacities	10	22 (69%)	32	18 (56%)
Peripheral opacity	44	19 (30%)	63	19 (30%)
Hilar opacity ..	5	11 (69%)	16	11 (69%)
No radiographic abnormality	0	6	6	6
Total ..	87 (32%)	189 (68%)	276	168 (61%)
Anatomical situation of lesion on radiograph:				
Right upper lobe	26	39 (60%)	65	35 (53%)
,, middle ,,	3	8 (73%)	11	7 (63%)
,, lower ,,	9	48 (84%)	57	41 (72%)
Left upper ,,	37	34 (48%)	71	28 (39%)
,, lower ,,	5	37 (88%)	42	35 (83%)
Hilar region ..	5	11 (69%)	16	11 (69%)
Whole left lung	0	5	5	4
,, right ,,	2	1	3	1
No radiographic abnormality	0	6	6	6
Total ..	87	189	276	168
Haemoptysis present	29	93 (76%)	122	88 (72%)
,, absent	58	96 (62%)	154	80 (52%)
Total ..	87	189	276	168

"Normal" and "abnormal" bronchoscopy refer to the macroscopic appearances of the bronchi only.

With regard to the type of radiographic abnormality there was a striking contrast between the proportion of abnormal bronchoscopic findings in patients with radiographic evidence of atelectasis (88%) and those with a circumscribed peripheral opacity (30%). The figures for a uniform lobar or segmental opacity (74%) and for patchy lobar or segmental opacities (69%) were, however, only slightly lower than those for atelectasis. In the last group of six cases,

shown in Table I, bronchoscopic evidence of tumour was found in the absence of any radiographic abnormality.

The anatomical situation of the lesion on chest radiography also influenced the proportion of abnormal bronchoscopic findings. The examination was of much greater diagnostic value in tumours of the right lower lobe (84%) and the left lower lobe (88%) than in tumours of the right upper lobe (60%) and the left upper lobe (48%), the figure for the right middle lobar tumours (73%) and hilar tumours (69%) being intermediate.

The proportion of cases in which a positive biopsy was obtained showed a similar correlation with the type and the site of the radiographic abnormality (Table I). The highest figure was recorded in cases with atelectasis (83%). Those for a uniform lobar or segmental opacity (56%), patchy lobar or segmental opacities (56%), and a hilar opacity (69%) were slightly lower, but in patients with a circumscribed peripheral opacity a positive biopsy was obtained in only 30%. Tumours of the lower lobes more often yielded a positive biopsy (right 72%, left 83%) than tumours of the upper lobes (right 53%, left 39%). The figure for right middle lobar tumours was 63%.

Results of Bronchoscopic Examination in Relation to Occurrence of Haemoptysis

The relationship between haemoptysis and the bronchoscopic findings is also shown in Table I. Of the 276 patients with bronchogenic carcinoma, 122 (44%) gave a history of haemoptysis: 93 (76%) of them had a macroscopic abnormality at bronchoscopy as compared with 96 (62%) of the 154 patients without haemoptysis. This difference is not statistically significant. In most cases the haemoptysis was slight but repeated, often occurring daily, usually in the mornings, for a week or longer. Of the six cases of bronchogenic carcinoma with normal chest radiographs five had haemoptysis, which was the sole indication for bronchoscopy, and the sixth had a paralysed vocal cord.

Results of Bronchial Biopsy in Relation to Macroscopic Appearances at Bronchoscopy

When tumour tissue was visible at bronchoscopy, bronchial biopsy was positive in 94% of cases (Table II). When a bronchus was completely stenosed but no actual tumour tissue was visible the figure was only slightly lower (85%). When, however, the stenosis was incomplete, it fell sharply to 39%. In the 87 cases with no visible abnormality at bronchoscopy, biopsy was performed in 62 and a positive result was obtained in 12 (20%). This surprisingly high figure was achieved by the technique of "blind biopsy" already described. The 25 cases in which biopsy was omitted were all investigated before the value of "blind biopsy" was appreciated.

TABLE II.—*Bronchogenic Carcinoma. Results of Bronchial Biopsy in Relation to Macroscopic Appearance at Bronchoscopy*

Biopsy	Visible Tumour	Complete Stenosis	Partial Stenosis	No Macroscopic Abnormality	Total
Positive..	125 (94%)	17 (85%)	14 (39%)	12 (20%)	168 (61%)
Negative	8 (6%)	3 (15%)	22 (61%)	50 (80%)	83 (30%)
Total	133 (100%)	20 (100%)	36 (100%)	62 (100%)	251 (91%)
Not taken	—	—		25	25 (9%)

The manner in which the diagnosis of bronchogenic carcinoma was confirmed in the 108 cases in which a bronchial biopsy was negative or was not performed is shown in Table III.

TABLE III.—*Manner in which a Diagnosis was Made in the 108 Cases of Bronchogenic Carcinoma with a Negative Bronchial Biopsy*

Histological Evidence		*Clinical Evidence*	
Cervical gland biopsy ..	15	Metastases elsewhere ..	20
Axillary ,, ,, ..	2	Paralysed vocal cord or diaphragm	3
Skin biopsy	3	Progressive weakness and death	20
Carcinoma at thoracotomy	33		
,, ,, necropsy	12		

The prospects of obtaining confirmation of a diagnosis of bronchogenic carcinoma by bronchoscopy and bronchial biopsy are influenced by three factors: (1) the type of radiographic abnormality, (2) the anatomical site of the tumour, and (3) the nature of the bronchial lesion.

Type of Radiographic Abnormality

When there is definite radiographic evidence of atelectasis a significant abnormality is almost invariably seen at bronchoscopy. The usual finding in this type of case is complete obstruction of the related bronchus either by tumour tissue within the lumen or by compression and invasion of the bronchial wall by surrounding tumour. Bronchial biopsy in these circumstances is technically easy and usually positive. With either a uniform or patchy lobar or segmental opacity the bronchoscopic abnormalities are similar to those found with atelectasis, but bronchial obstruction is more often incomplete, in which case tissue for biopsy may be difficult to obtain and negative results are rather more frequent.

With a circumscribed peripheral opacity, as would be expected, the bronchoscopic appearances are often normal. In a few cases, however, one of the larger bronchi may be compressed or invaded by a metastatic gland or by a proximal peribronchial extension of the tumour. In such cases an abnormality will be seen at bronchoscopy and a positive bronchial biopsy may be obtained. Even when the bronchoscopic appearances are completely normal, however, histological proof of the diagnosis may be obtained by "blind biopsy." Accurate radiographic location of the lesion is vitally important to ensure that the tissue is taken from the lobe or segment involved. "Blind biopsy" is not devoid of risk, as perforation of the bronchial wall may result in severe haemorrhage from a bronchial artery, pneumothorax, or mediastinal emphysema. Evidence that a bronchus has been perforated is occasionally provided by the presence of lung tissue in the biopsy specimen. If, however, facilities are readily available for the treatment of these complications, the danger to the patient is slight and is more than offset by the valuable assistance a positive biopsy can provide in the patient's future management.

When the radiographic abnormality is a true hilar opacity—that is, not merely a pulmonary opacity superimposed upon a normal hilar shadow—bronchoscopic examination often shows a significant abnormality. In this group of cases the earliest finding is narrowing of one of the major bronchi, often a main bronchus, by external pressure from malignant glands. Bronchial biopsy is difficult and sometimes negative at this stage. In many cases, however, the glands have ulcerated through the bronchial wall by the time bronchoscopy is undertaken. Frank tumour tissue can then be seen and a positive biopsy is readily obtained.

In our six recorded cases of bronchogenic carcinoma showing no abnormality of the chest radiograph the lesion in five cases involved the main carina and one or both main bronchi, but in one case it involved the carina between the right middle and lower bronchi. The nature and the situation of the lesions suggested that they were due to invasion of the bronchial wall by malignant glands. The feature common to these six cases and, presumably, to all other cases of bronchogenic carcinoma with normal radiographic findings is the absence of any important degree of bronchial obstruction, which, if present, would, of course, produce a radiographic abnormality.

Anatomical Site of Tumour

As the upper bronchi are less readily accessible to bronchoscopic vision, it is not surprising that tumours in the upper lobes were, in this series, less frequently detected by bronchoscopic examination than those in the middle and lower lobes. In general, the left upper bronchus is slightly more difficult than the right to examine with reflecting telescopes, particularly if the lobe is shrunken, and this is presumably the reason why bronchoscopic examination was less informative in the detection of upper lobe tumours on the left side (48%) than on the right (60%). The same

general observations apply to bronchial biopsy. Although the use of lateral biting forceps undoubtedly facilitates the removal of tissue from within the upper bronchi, the right apical and the left apico-posterior segmental orifices can seldom be reached even with those forceps unless the upper bronchus is displaced downwards. Tumour tissue in the main, intermediate, and lower bronchi, on the floor of the upper bronchi, and within the orifices of the lingular, middle, and basal bronchi can be easily removed with "straight" forceps, but the lateral biting type is preferable for biopsy from within the upper and apical (lower) bronchi, and from a partially stenosed main, intermediate, or lower bronchus.

Nature of Bronchial Lesion

In certain types of bronchial lesion problems of interpretation may arise. For example, a lower bronchus partially stenosed by surrounding tumour may be difficult to distinguish from a normal but unusually narrow lower bronchus, a phenomenon which is commoner on the left side and is sometimes related to the presence of a pleural effusion. In such cases it should be borne in mind that the lumen of a malignant bronchial stenosis, unlike that of a normal bronchus, is seldom truly circular and does not show the normal variation in calibre with respiration.

Abnormal rigidity of the main, intermediate, or lower bronchi due to peribronchial infiltration by tumour can undoubtedly be detected with the bronchoscope; but this does not provide reliable evidence of malignant disease, and too much significance should not be attached to it unless it is accompanied by bronchial narrowing.

Subcarinal widening by malignant bifurcation glands, an important contraindication to thoracotomy, may also present difficulties in interpretation. Points of value in confirming the presence of this abnormality are asymmetry of the widening on the two sides, narrowing of the lumen of one or both main bronchi, and local protuberances caused by neighbouring glands at the junction of the anterior or posterior ends of the main carina with the bronchial wall.

Bronchial biopsy is technically easier and its results are more reliable when the specimen is taken from frank tumour tissue or a complete bronchial stenosis than when taken from a partial stenosis. The likely reason for this is that with a partial stenosis the tumour, which in these cases is usually invading the bronchus from its external aspect, may not have penetrated the whole thickness of the bronchial wall and therefore will not be included in the biopsy specimen unless a deep bite can be taken.

It may perhaps seem rather surprising that every biopsy of frank intrabronchial tumour tissue in our series was not positive. The occasional negative results in such cases were probably due to superficial necrosis of the intrabronchial portion of the tumour rendering it histologically unrecognizable. This difficulty can be overcome by removing the necrotic material gently by suction and then taking tissue deeply from the tumour mass. If the specimen sinks in saline it is unlikely to be necrotic.

The significance of a negative bronchoscopic examination in the exclusion of tumour may be extremely difficult to assess. In only one type of case (a patient with a normal chest radiograph who is submitted to bronchoscopy on account of haemoptysis) is a negative finding completely reassuring. In general, a diagnosis of tumour is very improbable if the bronchus supplying an atelectatic lobe or segment is clear, but such a conclusion is not valid in every case. With patchy lobar and segmental opacities, which in cases of bronchogenic carcinoma are usually due to pulmonary infection distal to a partial bronchial obstruction, a negative bronchoscopy virtually excludes tumour provided there is no associated hilar enlargement and the pulmonary opacity clears completely on chemotherapy. A uniform lobar or segmental opacity without atelectasis, although generally due to infection, is occasionally produced by a tumour mass occupying a whole lobe or segment, and in such cases a negative bronchoscopy may be of little diagnostic value. With a true hilar opacity and a circumscribed peripheral opacity negative findings at bronchoscopy are of no significance whatever in the exclusion of tumour.

In view of the fact that tumours of the lower and middle lobes are easier to detect than those involving the upper lobes, negative bronchoscopic findings can be more readily accepted as evidence against a diagnosis of tumour when the radiographic abnormality is in the middle lobe or in one of the lower lobes.

2. Bronchiectasis

There were 118 patients shown by bronchography to have bronchiectasis. These patients were also examined by bronchoscopy as part of the investigation of their respiratory symptoms. In most cases bronchoscopy was carried out immediately before bronchography to ensure that the bronchi were clear of secretions. Apart from this purely technical indication the reason for bronchoscopy in these cases was to discover whether the bronchiectasis was secondary to an obstructive lesion in a main bronchus such as a tumour or a fibrous stenosis.

In neither respect has bronchoscopy been of much positive value. The general standard of bronchography was not improved by preliminary bronchoscopy, and an abnormality of a major bronchus was found in only 3 of the 118 cases. In each case the lesion was a fibrous stricture of a lower bronchus; all three patients were men over 50. In all three the stricture was clearly shown on the bronchogram and would not have been overlooked had bronchoscopy been omitted.

These observations suggest that bronchoscopy is not a very profitable routine investigation in bronchiectasis. If, however, surgical treatment is contemplated bronchography should invariably be supplemented by bronchoscopy, as failure to discover a fibrous stenosis in a major bronchus might seriously prejudice the result of the operation.

3. Pulmonary Tuberculosis

Bronchoscopy was performed in 132 patients with pulmonary tuberculosis, in 89 to exclude tumour and in 43 to exclude endobronchial tuberculosis.

Of the 89 patients in whom a diagnosis of tumour was suspected, 68 were examined by bronchoscopy because the radiographic appearances were in keeping with either tuberculosis or tumour and because tubercle bacilli had not at the time been isolated from the sputum. A further nine had tubercle bacilli in the sputum before bronchoscopy, but the abnormality of the chest radiograph was so suggestive of tumour that a double diagnosis was suspected. In three patients, despite a negative sputum, a confident diagnosis of tuberculosis had been made from the chest radiograph, but it was subsequently deemed necessary to carry out bronchoscopy in view of a poor response to chemotherapy. In eight patients slight haemoptysis raised the suspicion of a tumour, although the radiographic abnormalities were merely those of minimal, apparently inactive, tuberculosis. The indication for bronchoscopy in the remaining patient, with an old-standing fibrotic tuberculous lesion, was peripheral neuropathy thought to be based on malignant disease.

In this group of 89 patients tumour was found at bronchoscopy in three. Two of these developed new opacities in the chest radiograph after the completion of treatment for active pulmonary tuberculosis. They were submitted to bronchoscopy, as sputum examination was negative for tubercle bacilli and the radiographic appearances were more suggestive of tumour than of a reactivation of tuberculosis. The third patient developed a new opacity in the right upper lobe while still receiving antituberculous chemotherapy, although the opacities elsewhere were improving and the sputum had become negative. In a fourth patient bronchoscopy was normal but a diagnosis of bronchogenic carcinoma was subsequently made by rib biopsy. He had presented with what appeared to be a tuberculous cavity at the right lung apex with fibrotic tuberculous shadowing in the left upper lobe. In only four other patients in this group was bronchoscopy abnormal. The

findings in these patients were ulcerating tuberculous glands (two cases), bronchial stricture, and atresia of the left lower bronchus.

Of the 43 patients in whom a diagnosis of tuberculosis had already been established and who were examined by bronchoscopy on account of suspected bronchial complications, nine showed significant abnormalities. In five patients there was evidence of glandular ulceration through the bronchial wall. In a further patient a bronchus was compressed by a gland but not ulcerated, and in three others a healed bronchial stricture was found.

Of the total of 132 cases of pulmonary tuberculosis submitted to bronchoscopy, 89 were classified as active (70 sputum-positive) and 43 inactive. In 8 (9%) of the active cases there was bronchial involvement secondary in every instance to glandular ulceration. This figure, of course, relates to a highly selected group and in no way represents the real incidence of bronchial complications of pulmonary tuberculosis, which must be very much lower. None of the patients had acute tuberculous endobronchitis. A bronchial stricture, probably related to a previous tuberculous infection, was found in four cases, one with active and three with inactive pulmonary tuberculosis.

Value of Bronchoscopic Examination in Patients with Pulmonary Tuberculosis

There were three positive results in the 89 bronchoscopic examinations to exclude tumour (3.4%). The large number of negative examinations is undoubtedly a reflection of our anxiety not to overlook a tumour. The same cautious attitude is also responsible for the fact that in no fewer than 9 of the 86 patients without evidence of tumour at bronchoscopy the possibility of malignant disease was considered strong enough to warrant thoracotomy. If we had been prepared to wait a few weeks for a positive culture of the sputum for tubercle bacilli 35 patients might not have required bronchoscopy or thoracotomy. In some cases, however, a delay of this length might have had serious consequences. Moreover, the radiographic appearances in many of our other patients with proved tumours were consistent with tuberculosis, and, if the indications for bronchoscopy in this type of case had been relaxed, errors and delays in diagnosis would have been much more numerous. This consideration, together with the results of work by Sakula (1955), who concluded that a combination of tuberculosis and tumour was more frequent than could be accounted for by chance association, has convinced us that our present policy is correct, and we would be reluctant to alter it.

The commonest abnormality found on bronchoscopic examination of tuberculous patients in this series was bronchial ulceration by caseous glands complicating a primary tuberculous infection. Tuberculous endobronchitis in association with post-primary pulmonary tuberculosis was not seen. Although there has undoubtedly been a sharp decline in the prevalence of this condition in recent years the total absence of this type of bronchial lesion in our series could equally well be explained by the nature of the clinical material, in that few of the patients had large numbers of tubercle bacilli in the sputum, and some had received antituberculous chemotherapy for a few weeks before bronchoscopic examination.

A bronchial stricture, presumably of tuberculous origin, is a not uncommon incidental finding at bronchoscopy.

4. Other Conditions

The final diagnosis in the 458 patients outside the three main groups already discussed was as follows:

Pneumonia	136	Benign pulmonary atelectasis	13
Chronic bronchitis	100	Pulmonary infarction	12
Haemoptysis—cause not determined	57	Sarcoidosis	11
Pleural effusion or empyema (non-malignant)	28	Metastatic pulmonary tumours	11
Benign tumours and cysts	16	Spontaneous pneumothorax	7
		Miscellaneous conditions	67

By far the commonest reason for bronchoscopy in these cases was to exclude a bronchogenic carcinoma, which had been suspected from (*a*) the symptoms—for example, haemoptysis; (*b*) the clinical features—for example, finger-clubbing; (*c*) the radiographic appearances; or (*d*) an unsatisfactory response to treatment.

Pneumonia.—In some cases of pneumonia bronchoscopy was advised where there was slow or incomplete resolution of the consolidation after adequate chemotherapy. Bronchoscopy was usually confined to such cases, as in our experience complete clearing of consolidation on the chest radiograph is very seldom associated with an underlying tumour, and it is clearly impracticable to examine by bronchoscopy every patient with pneumonia.

Chronic Bronchitis.—Haemoptysis is a common feature in chronic bronchitis. It is also, however, a frequent presenting symptom in bronchogenic carcinoma, and this largely accounts for the fact that we submitted to bronchoscopy 100 patients in whom no abnormality other than chronic bronchitis was eventually found. Another factor contributing to the frequency of bronchoscopy in chronic bronchitis was the large number of such patients who on account of repeated respiratory infections showed on chest radiography pulmonary opacities and pleural thickening, consistent with the presence of a tumour. It is impracticable to investigate by bronchoscopy every patient with chronic bronchitis who develops haemoptysis or has a radiographic opacity. Some degree of selection must be exercised. In the case of haemoptysis, however, bronchoscopy must always be advised when the bleeding persists for a few days.

Haemoptysis—Cause Not Determined.—Although bronchoscopy was negative in 57 patients who presented with haemoptysis and a negative chest radiograph in the absence of chronic bronchitis, five other patients in the same category were found to have tumours. For this reason we now regard haemoptysis as a more compelling indication for bronchoscopy if the patient does *not* give a history of chronic bronchitis.

Pleural Effusion.—There were 52 cases of either pleural effusion or empyema in the series of 980 bronchoscopic examinations. Twenty-four had an underlying bronchogenic carcinoma, but in only four was the pleural abnormality due to malignant involvement. In the other 28 cases the pleural effusion was simple inflammatory in origin, usually tuberculous. Bronchoscopy was carried out in these patients either because they were in the older age groups or because there was insufficient evidence to support a tuberculous aetiology.

Benign Tumours and Cysts.—The indication for bronchoscopy in all cases was a radiographic opacity in the lung or mediastinum. Four cases of bronchial adenoma were included among the benign tumours, but in only one was the diagnosis made by bronchoscopy. In the remaining three the tumour was situated peripherally in the lung.

Other Cases.—The remaining cases were examined by bronchoscopy for a variety of reasons. In pulmonary infarction, for example, the combination of haemoptysis and a pulmonary or pleural opacity often suggested the presence of a tumour. In spontaneous pneumothorax a persistently atelectatic lobe was the usual indication. The patients who eventually proved to have benign pulmonary atelectasis, sarcoidosis, or metastatic pulmonary tumours required bronchoscopy because the radiographic appearance could not be distinguished from that of a primary bronchogenic carcinoma.

Significance of Haemoptysis with a Normal Chest Radiograph

In our survey 93 patients had a normal chest radiograph following haemoptysis, and a bronchogenic carcinoma was found at bronchoscopy in five. In none of the 38 patients aged 40 or under was a tumour found, but in the 55 patients over the age of 40 a tumour was seen in five. If the chest radiograph in each of these five cases was indeed normal this would emphasize the danger of accepting a normal chest radiograph as excluding a bronchogenic carcinoma.

An attempt was therefore made to determine whether the chest radiographs of the five patients (seen between 1952 and 1956) were considered normal by those accustomed to interpreting chest radiographs. This investigation is reported in detail elsewhere (Somner and Sklaroff, 1958). The five radiographs were presented to 18 observers along with those from three similar cases encountered during 1957 (not included in the general analysis in this paper) and that of a ninth patient who presented with a paralysed vocal cord but without haemoptysis. The observers were asked to review these nine radiographs along with 60 others (in random order) from patients also with haemoptysis who had been examined by bronchoscopy to confirm or exclude a bronchogenic carcinoma.

Although we classified fewer hilar shadows as enlarged than the panel of observers *as a whole*, there was no evidence that our classification of "normal" hilar shadows was different from that of the *majority of observers*. Moreover, since the 18 observers did not need to make clinical decisions, they may have been inclined to be more positive in their assessment of abnormality. It is therefore concluded that our standard of interpretation of a normal hilar shadow was similar to that found among the group of observers.

The final diagnosis in the 93 cases was as follows: bronchogenic carcinoma, 5; hypertension, 7; bronchitis, 20; bronchiectasis, 9; mitral stenosis, 1; foreign body, 1; no cause, 50.

In view of the relative frequency of bronchogenic carcinoma in this group of cases we consider it advisable that all patients with haemoptysis, especially males over the age of 40, should be examined by bronchoscopy to exclude bronchogenic carcinoma even when the chest radiograph is normal, unless there is some pre-existing respiratory or cardiovascular disease which could possibly account for it.

Summary

In an attempt to clarify the indications for bronchoscopy, in particular where there is a possibility of bronchogenic carcinoma, an analysis was made of 1,109 patients examined during 1952 to 1956.

In 276 patients with a bronchogenic carcinoma the results of bronchoscopic examination and bronchial biopsy were analysed in relation to the radiographic appearances and the presence or absence of haemoptysis. A visible abnormality at bronchoscopy was found in 189 (68%) and histological evidence of the disease was obtained by bronchial biopsy in 168 (61%). The value of "blind" biopsy in obtaining histological evidence of carcinoma when the bronchoscopic appearances were normal is stressed. The diagnostic value of bronchoscopy was found to be related both to the type of radiographic abnormality and to its anatomical situation. The finding of an abnormality at bronchoscopy was not in general related to the presence or absence of haemoptysis, but in six patients with tumours and a normal chest radiograph haemoptysis was the presenting feature in five.

In the 118 cases of bronchiectasis reviewed it was concluded that bronchoscopy was not an essential part of the investigation unless surgical treatment was contemplated. Out of 132 cases of pulmonary tuberculosis examined by bronchoscopy an active endobronchial lesion was found in six patients with primary tuberculosis and a bronchogenic carcinoma in three.

Our thanks are due to Professor John Crofton and Dr. Christopher Clayson for permission to include those patients under their care and for help in the preparation of the paper, and to Miss Winifred A. M. Tait for secretarial assistance.

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TATTOOING IN THE SERVICE OF SURGERY

BY

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The practice of tattooing (Polynesian, *ta tau*, to mark) is undoubtedly of very ancient, prehistoric origin. In caves in Western Europe hollowed stones for grinding coloured clays are to be found; such colours were, and indeed in some regions still are, used for surface decoration (cp. woad in Britain), but it seems likely that, perhaps as the result of an accident, it was discovered that the implantation of the clay, or of charcoal from a fire, into a cut or puncture produced a permanent pattern which avoided frequent renewals. An early historical reference to the practice is to be found under the Mosaic Law in Leviticus, xix. 28, "Ye shall not make any cuttings in your flesh . . . nor print any marks upon you."

Early Tattooing

Although at first probably purely decorative, tattooing later acquired religious, tribal, and social significance, or in some cases was merely of horrific intent. The cult

FIG. 1.—Keloid scar tattooing on an Australian aboriginal produced by the method described in the text.

varied greatly. Thus in Polynesia it was a mark of puberty; among Arabs, infants were tattooed as a simple ornament or means of recognition; for the American Indians and the Australians it was a sign of the tribe or family; while the Kaffirs employed it as a decoration for bravery. The most extensive tattooing is found on the Laos of Indo-China, where the division into "black paunch" and "white paunch" areas depends upon the tattooing of the abdominal wall, but, in addition, the thighs, legs, and breasts are often completely covered with fantastic animal figures. In

Polynesia, too, large areas of the body were covered, whereas the Maoris concentrated on the face. Among dark-skinned races where ordinary pigment tattooing would be almost invisible the tendency is to produce pale keloid scarring by rubbing clay into the cuts forming the pattern (Fig. 1).

In Japan the practice became a high art, and the most varied and delicate colours were produced; there its original function was neither ceremonial nor symbolic, but in lieu of clothing. Apart from decorative and symbolic uses tattooing has had utilitarian employment to identify slaves and criminals; in the British Army until 1879 the letter D was tattooed on a deserter and B C on a bad character. Much more recently the suggestion has been made, and I believe carried into practice, that medical information, probably in code, might be tattooed on patients liable to attacks of coma—for example, in hypoglycaemia—or post-operatively when some unexpected or additional structure had been dealt with—for example, an appendicectomy in an operation for gastric ulcer.

There is no doubt that in this country tattooing, even of soldiers and sailors, among whom it was very popular not so long ago, is on the decline, but I was surprised to learn, by personal acquaintance with one, that the "young bloods" of late Victorian times were often extensively and expensively tattooed. The scene in this case, in a greyish-green monotone, was a classical one, reminiscent of a Leighton painting, extending all over the torso. It is the only tattoo in which I have seen shading and shadow most realistically represented. The tattooist evidently deserved the 250 guineas which he was paid in the 1890's for work occupying over three weeks. Other ambitious tattoos include a hunting scene in full colour around the torso of a woman (for tattooing is not exclusively restricted to males) excellently executed, a picture on the back of a doctor representing a tiger stalking through the jungle, which was a real work of art, and a large tropical butterfly on the chest of an officer, a most exquisite piece of work (Japanese) in which colours rarely seen, such as purples, blues, greens, yellows, etc., were beautifully combined. I have come across a large number of quite attractive tattoos of rather less extent which nevertheless displayed a good deal of artistry and a fairly wide range of colouring from the common red through the spectrum to the rare pure blue and purple.

But most tattoos are much less skilful: we are all well acquainted with the entwined hearts, the clasped hands, the initials of the loved one or the announcement "I love Kate," the regimental and other crests, flags, ships, the female form, and so on. Many of these are in the two common colours blue-black (Indian ink) and red (cinnabar); the materials used by the professional tattooists for the other colours are kept a close secret, and so it has been necessary to experiment with some of the modern synthetic dyes in an attempt, not entirely successful, to discover what is available.

In the surgical as opposed to the ornamental uses of tattooing the main object is, of course, a cosmetic one, and it can be employed as an adjunct to or a substitute for plastic surgery. It is, however, sometimes used therapeutically as a treatment for certain skin diseases, especially pruritus (Turell, 1941). Several papers have been published, chiefly in the United States (Cantor, 1943), on this aspect of tattooing, but the present article is concerned only with its cosmetic use.

Colours

Of the colours already noted, the ones most needed for this purpose are black and brown for hair, red for lips, pink and brown for skin, dark blue for beard stubbling, and white for tattooing down other colours.

The material used for "black" tattooing is some form of carbon, lamp black, Indian ink, but, as is well known, owing to the selective absorption of incident light by the overlying tissues this really gives a deep blue-black result, which is a poor match for black hair. Remembering that the intensely black patches of a melanoma are seen under the microscope to be produced by a dark umber pigment, I have used a combination of the dye "golden umber" with a little carbon and thus achieved a better approximation to a true black. The common red pigment is cinnabar (mercuric sulphide), sometimes called Chinese red; this has the virtue of being permanent, whereas some of the synthetic dyes tend to become faint and even to disappear entirely in the course of time. It is, however, stated that mercury poisoning has followed the tattooing of large areas, but I have no record of this. In personal trials it was found that after 15 years "irgalite red 36" and "lake fast rubine" had disappeared, while "red oxide R. 93A" and "irgalite orange P" remained, although somewhat reduced in intensity. Of the brown pigments, both "iron oxide" and "golden umber" were reasonably permanent. The most satisfactory and permanent of several "whites" tested proved to be titanium oxide when used for tattooing out and reducing colour. It is worth noting that the chromium greens, yellows, and reds all caused rather violent immediate reactions; the "red chrome R 5" actually sloughed out, but this was possibly due to a personal idiosyncrasy.

FIG. 2.—Photomicrograph of section of skin tattooed with cinnabar. In a black-and-white reproduction the refringent pigment particles are difficult to distinguish; some are indicated by arrows.

FIG. 3.—Higher magnification of Fig. 2 to show perivascular collection of pigment.

All tattoos tend to decrease in intensity with time. For the first few weeks this is fairly rapid and may be due to transference of some of the pigment to neighbouring lymph nodes, to loss of pigment which reached no further than the epidermis—as pointed out by Matthews (1947)—and possibly to a certain amount of local fibrosis. Later there is a slower decrease accompanied by some local diffusion of the pigment, so that the margins of the tattooed area become less distinct; as mentioned above, with some materials the dye itself seems to be slowly absorbed or decolorized.

The depth to which the pigment is carried varies with the technique and the instrument used. The permanent colour is always in the dermis or subdermis, as is shown in the photomicrograph (Figs. 2 and 3) of a section in which the pigment from a red (cinnabar) tattooed area appeared as refringent particles in both these situations, the deeper masses being aggregated around the vessels. Without colour reproduction it is difficult to distinguish the particles, some of which have therefore been marked with arrows. Dr. Shore has kindly reported upon this section as follows: "There are many pigment granules in the dermis, all apparently within the cytoplasm of phagocytic cells. These pigment-containing cells are scattered fairly evenly in the middle dermis, but denser collections are present in relation to the small arterioles. No pigment is seen in the dermal papillae or in relation to the secretory portion of the sweat glands." This tattoo was of many years' duration; the particular technique used is unknown.

Antiseptic Precautions

Although some of the professional tattooists nowadays make a perfunctory application of some antiseptic to the skin and the needles, for the most part, especially in seaports abroad, no sort of antiseptic precautions are taken. The surprising thing is that so few seem to go grossly septic, but when they do the result can be both serious to the subject and disastrous to the tattoo. In one case seen many years ago the heart-rending message "I LOVE KATE" was outlined in pustules down the forearm; some of the pigment particles came away in the dressings which were applied, and the final result was the persistent message in a bizarre mixture of white scar and patchy pigment. It is well known that syphilis, tubercle, and other diseases have been inoculated by the tattooing needles. In surgical practice the usual aseptic technique will of course be applied.

Small areas can be tattooed in relatively insensitive parts without any anaesthetic, the discomfort being minimal; in surgical work, however, for large sensitive areas either a local or a general anaesthetic is necessary. If the former it is well to massage any excess of fluid away before the needles are used, otherwise it is difficult to judge depth and intensity. Many of the decorative tattoos are done, with or without consent, while the subject is under the influence of alcohol—evidently a good anaesthetic for this purpose.

Originally all tattooing was, of course, done by hand, employing a small bundle of bone (later metal) needles or points. This hand method can still be employed by the surgeon if the area to be covered is small; usually, however, a vibratory machine is used. There are several patterns—electromagnetic, sol noid, synchronous, or even mechanical clockwork. The needle points, 6 to 10 in number, are usually protected by an adjustable guard which enables the depth of penetration to be varied according to the thickness of the dermis and epidermis at varying sites. In some types of machine the actual needle stroke is controllable. About 2 to 3 mm. penetration is an average. This part of the instrument must be sterilizable. The powdered pigment is mixed with a little water to form a paste in a container which can be placed in the ordinary instrument sterilizer. I have not found this alters the colour of the pigments I have used, but Matthews (1947), for fear of such a change, sterilizes his pigments with absolute alcohol. The addition of a small quantity of penicillin to the paste before use may be an additional precaution, unless the patient is found to be sensitive to it.

Technique

The area to be tattooed is prepared and covered with the paste through which the needles work. Judging the intensity of the coloration is a great difficulty; there are probably few surgeons who get enough experience to be able to do this without a lot of trial and error. From time to time all the paste, to which a certain amount of blood is now added, is wiped off and oozing of blood arrested so that the depth of colour can be estimated. Even so, it is not at all easy to be certain of the final result; for the multiple punctures and hyperaemia of the skin tend to obscure the pigmentation. Furthermore, allowance must be made for the early fading noted above, a factor which is always rather unpredictable. In some cases it may be considered wise to call in the help of a professional tattooist, whose greater experience will enable him to achieve a nearer colour match. I am told that some professionals are now turning their attention to cosmetic as distinct from decorative tattooing. It is certainly better to underdo rather than overdo the process, for at a subsequent session more pigment can be tattooed in, but it is much more difficult, although not always impossible, to reduce the intensity.

During the tattooing, the skin should be kept stretched and steady, but care must be taken not to distort it. The area to be covered must be marked out, and as such markings may be obscured when the paste is applied it is sometimes of value to use a template. This is particularly so when a definite line has to be followed—for example, an eyebrow or the red lip margin. Fig. 4 shows an easily made template for tattooing the "cupid's bow" on the lip; it is of sheet metal; if the subject indicates her wishes with a lipstick the template can be fashioned to suit (Fig. 5). A second backing sheet (with a notch for the frenum if this is present) fits into the bucco-labial recess to give even counter-pressure. Eyebrows, too, can be marked with grease-paint to the patient's satisfaction and the curve copied on a template to guarantee accuracy. Fig. 6 is a print from a colour photograph of a case where an ugly irregular scarred lip with practically no red margin followed a hare-lip operation in infancy. The result shown, although the reproduction unfortunately loses considerably from lack of colour, was achieved by using a template of the sort described. The

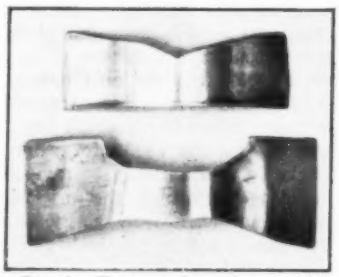

FIG. 4.—Sheet-metal templates used for tattooing red border of lip.

FIG. 5.—Showing use of templates. The notch in the upper margin is to clear the columella if the lip is very shallow.

exact tinting of skin grafts in conspicuous positions to match their surroundings is difficult; although improvement is usual, perfection is rare.

Many other possible indications for tattooing will present themselves from time to time. Thus beard-stubbling can be imitated in dark-haired men with pallid facial grafts or scars; nails (painted or otherwise) can be simulated after amputation of the ends of digits, usually fingers but nowadays also toes; while, following plastic reconstruction of the breast, if the nipple has not been transplanted, a nipple and areola tattooed in may mollify the patient's embarrassment. "Some patients are extremely sensitive about sacrificing the umbilical pit" (Max Thorek); this surgeon transplants the umbilicus when performing plastic reduction of the abdominal wall, but this contingency could alternatively be dealt with by tattooing. An unusual demand came some years ago from a Chinese lady who, as the result of a motor accident, was left with a very conspicuous wide scar running right through the hair margin some distance into the scalp. This was an aesthetic calamity, for the framing of the face in a perfect unbroken square of intensely black hair is, so I was informed, one of the most important criteria of beauty in her country. The case was dealt with by surgery, since at that time no method of producing a jet-black tattoo was available; the incident, however, started the search, not yet satisfactorily completed, for new pigments by which this could be achieved.

FIG. 6.—Print from colour photograph of a case of hare-lip described in the text in which templates were employed. Before tattooing practically no red margin was visible. The colour original shows an excellent colour match (without make-up). The pigment used was a mixture of "red oxide R.93A" and "irgalite orange P."

Removal of Tattoo Marks

As already mentioned, complete tattooing out is almost impossible, but a reduction of colour intensity may be accomplished by over-tattooing with titanium oxide. This intensely white pigment appears from our tests to be remarkably permanent and has greater "covering" value than other materials tried.

Removal of tattoo marks is often demanded, sometimes on account of a change in social status, sometimes because the tattooing was accidental and unwelcome—for example, after road and mining accidents with tar or coal-dust inclusion, or bomb incidents, which produced some rather fantastic examples, such as the pattern, in negative, of an ornamental iron railing on the bare back of a lady who was leaning against it at the time of the explosion. Then there is the embarrassment which a transfer of affection to "George" occasions when the tattoo declares that the lady "Loves Fred" (an actual example that required complete excision and skin-grafting to eliminate).

A linear accidentally tattooed scar can obviously be excised completely, but in most cases the area involved is too extensive to be dealt with in this way. It will be remembered that the pigment particles lie in the dermis and subdermal tissues, so that no superficial removal such as is produced by scarification (Kromayer, 1905), whether by sand-paper or the wire-brush technique (Eller and Eller, 1956), can be expected to be entirely satisfactory, however good such methods may be for surface lesions such as acne scars. Dermabrasion (Pegum, 1957) of this type would have to be carried into the deep layers of the dermis, allowing epithelization only from the sparsely scattered hair roots and skin glands, a very slow process which not only leaves a very conspicuous scarred area but often results in ugly keloid scars. The only satisfactory method is by complete excision followed either by sliding flaps or skin-grafting; in many areas a split-skin Thiersch graft is acceptable, but in others a full-thickness or pedicle graft is required. The moral is that, once a tattoo is in, the subject can never more be "without mark or blemish."

Conclusion

Apart from the chance of transferring diseases, the risks of tattooing are those of infection, avoidable in surgical practice; of local reaction to the pigments used, sometimes idiosyncratic, as in the case of chromic salts producing sloughing; of general poisoning, as recorded very rarely with mercuric salts; and, equally infrequently, of a much-delayed reaction. These late cases may occur many years after an uneventful tattoo (Bonnell, 1956)—especially, apparently, with the green chromic salts, if the subject comes into intimate contact with other chromic-containing material, such as paints, to which he appears to have become sensitive.

All these risks are, however, quite remote and should not debar the proper employment of an excellent method of overcoming many disfigurements.

Summary

A brief account of the historical development and decorative application of the common forms of tattooing is given and certain ambitious tattoos are described.

The pigments which may be employed in the surgical uses of tattooing are discussed, as is also their suitability for this purpose and their distribution in the skin.

The technique of tattooing by hand and mechanical methods is described, with an indication of possible surgical applications and of the assistance afforded in some instances by the use of templates.

The complications and risks of tattooing, both immediate and remote, are considered, and the long-term changes which occur are described.

The methods which may be employed in the removal of unwanted tattooing are discussed and their limitations indicated.

I am indebted to Mr. Clifford Evans, F.R.C.S., whose chemical knowledge was of great assistance; to Dr. J. H. Shore and the department of pathology, Charing Cross Hospital Medical School, for the pathological report and the photomicrographs; and to Miss Turnbull, of the photographic department of the hospital, for the photographs.

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The Sir George Earle Trophy for a notable achievement in the cause of industrial accident prevention has been awarded this year to Imperial Chemical Industries Ltd. This is the third time the trophy has been awarded. In 1956 the recipients were H.M. Inspectors of Factories, and last year it was awarded to the Birmingham and District Industrial Safety Group.

THE COURSE OF REITER'S SYNDROME

BY

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Reiter's syndrome in its fully developed form is characterized by an association of non-specific urethritis, arthritis, conjunctivitis, and a number of less constant features (Reiter, 1916). Cases of urethritis and arthritis alone have a course indistinguishable from the full syndrome and are therefore included in this study. This leads to difficulties in nomenclature which will be resolved only when the aetiology of this condition becomes known.

Clinical descriptions of individual attacks are many, but the natural history of the syndrome has received little attention and much remains unknown. Ford (1953), in an interesting paper, describes the history of 21 selected cases, the criteria being recurrent or chronic arthritis over a period of five years or more. It is my aim to record some observations on a large group of consecutive patients, many of whom have been followed for several years.

Present Study

This is based on the experience gained from 185 consecutive patients (182 male, 3 female) with Reiter's syndrome who attended the venereal disease clinic at St. Mary's Hospital, London, from 1942 to 1956 inclusive. A few had their first attack elsewhere, and in some the disease started before this study began. I saw 125 cases personally, and the rest were studied from their medical records. Of the 185 cases, 87 had arthritis associated with genital infection and 98 showed additional features, especially eye and skin involvement. Most of the patients received some form of treatment which might have influenced the natural course of the disease, but there is no good evidence that any current therapy can essentially alter the progress of Reiter's syndrome (Fowler and Knight, 1956).

Incidence in Hospital.—The incidence of the syndrome in relation to the total number of urethral infections seen in males at this clinic over the same period was 0.8% (22,010 cases of urethritis and 182 males with Reiter's syndrome). As the study is confined to hospital patients it is not thought that it necessarily reflects the incidence of the syndrome as it may occur in the general population. Apart from genital infections, bacillary dysentery has been associated with this syndrome, and it is of interest that similar incidence figures have been noted (Paronen, 1948).

Basic Data

The small number of females confirms the general experience that they are only exceptionally affected. In cases occurring after dysentery there is a much higher incidence in women (Paronen, 1948). Both white (164) and coloured (21) patients were affected, though the condition seemed to be less severe in coloured patients.

The social class and civil state of the patients are shown in Table I. Table II shows that the majority of patients in this series were sexually promiscuous and that casual sexual relationship prior to the onset of the genital infection leading to Reiter's syndrome was the rule. In two patients non-specific urethritis (N.S.U.) and arthritis was said to follow their first sexual contact.

Table III deals with the history of genital infection; it is apparent that a number of patients have a past history of venereal urethritis. Of the 16 who presented themselves with several features of the syndrome but no evident urethritis, 12 were found to have chronic persistent prostatitis and all gave a past history of gonorrhoea.

TABLE I.—*Social Class (Registrar-General's Classification) and Civil State of 185 Patients*

	Class					Civil State			
	I	II	III	IV	V	Single	Married	Divorced	Widowed
No.	3	5	55	80	42	107	68	7	3

TABLE II.—*Sexual Background (Obtained from Personal History and Past Record of Venereal Disease)*

Sexual Habits		Sexual Contacts before Onset of Reiter's Syndrome with	
"Promiscuous"	112	Wife/husband	17
Not promiscuous	41	Friend	25
No intercourse ever	2	Stranger/prostitute	99
Data incomplete	30	Homosexual	4
		"None"	2
		Data incomplete	38

TABLE III.—*Frequency of Past and Present Lower Urogenital Infection (in 185 Patients with Reiter's Syndrome)*

	Before 3 Months of Onset of Reiter's Syndrome	Within 3 Months of Onset of Reiter's Syndrome
Gonorrhoea	74	26
" with residual N.S.U.	—	67
N.S.U.	8	71
Haemorrhagic cystitis with N.S.U.	2	5
Urethritis of unknown diagnosis	11	—
No urethritis	90	16*

* 12 of these patients had asymptomatic chronic prostatitis.

The attacks which were closely associated with gonorrhoea were of special interest because of the now generally accepted view that the important aetiological factor is a non-gonococcal element rather than a gonococcal one (Harkness, 1949). In 67 patients penicillin apparently cleared the gonococci, leaving a residual urethritis which was followed by arthritis and sometimes by other symptoms of the syndrome. In 26 further cases no post-gonococcal urethritis followed penicillin; nevertheless a typical attack of arthritis, with or without conjunctivitis, developed a few days later and did not respond to penicillin. There seemed to be no clinical difference between attacks preceded by N.S.U., gonorrhoea with N.S.U., or gonorrhoea alone, and the significance of these findings is uncertain.

The age of onset ranged from 15 to 59 years, and 82% of attacks occurred between 20 and 40 (Table IV). The frequency of the principal signs and symptoms is recorded in Table V.

TABLE IV.—*Age of Onset of Reiter's Syndrome*

Age in Years	No.	Age in Years	No.	Age in Years	No.
15–	8	30–	41	45–	9
20–	34	35–	26	50–	2
25–	51	40–	12	55–59	2

TABLE V.—*Frequency of Principal Manifestations*

	No. Affected	
Genital infection:		
N.S.U.	71 (38·4%)	
Gonorrhoea with N.S.U.	67 (36·2%)	
"	26 (14·0%)	97·8%
Acute haemorrhagic cystitis with N.S.U.	5 (2·7%)	
Chronic prostatis without N.S.U.	12 (6·5%)	
Joint and tendon involvement:		
Polyarthritis	161 (87·0%)	
Monoarthritis	14 (7·5%)	100%
Arthralgia	10 (5·5%)	
Sacroiliitis	16 (8·6%)	
Achilles tendinitis	24 (12·9%)	19·9%
Other "	13 (7·0%)	
Plantar fasciitis	40 (21·6%)	
Eye lesions:		
Conjunctivitis	60 (32·3%)	
Iritis	21 (10·8%)	45·8%
Keratitis	5 (2·7%)	
Balanitis	38 (20·5%)	
Cystitis (non-haemorrhagic)	37 (20·0%)	
Keratodermia blennorrhagica	26 (14·0%)	
Stomatitis	11 (5·9%)	
Thrombophlebitis of legs	5 (2·7%)	
Subcutaneous nodules	3 (1·6%)	
Pericarditis	1 (0·5%)	

Latent Period

In a limited number of patients the periods between the relevant intercourse and the onset of urethritis on the one hand and between the onset of urethritis and the next manifestation of the syndrome were recorded, but as the data depend entirely on the patients' veracity and good memory, the figures should be treated with some reserve (Table VI).

TABLE VI.—*Latent Periods*

	No. of Cases	Mean Time (Days)
Sexual intercourse to onset of gonorrhoea	50*	6
Onset of gonorrhoea to onset of arthritis		12·7
Sexual intercourse to onset of N.S.U.	30	13·3
Onset of N.S.U. to onset of arthritis		14

* All these cases developed post-gonococcal N.S.U.

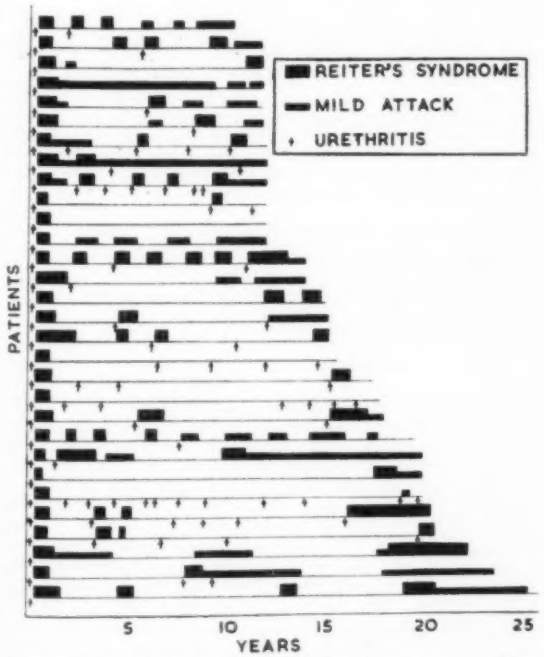
The duration of first attacks in 165 cases ranged from 3 weeks to 18 months (mean: 3.8 months), and in the remaining 20 cases the disease showed no clear-cut remission from the start for three or more years.

Follow-up

Eighty patients were observed for less than one year, mostly because they defaulted. In the majority of defaulters the attacks were mild, and it is possible that most of them did well subsequently; but even if one assumes the somewhat improbable event that all of them were cured, there are still over 50% of the total series known to have had repeated attacks or continued activity over a number of years. These findings give a less favourable picture than is sometimes suggested and emphasize the need for a long observation period (Table VII).

TABLE VII.—*Follow-up of Patients with Reiter's Syndrome*

Duration (Years)	No. of Patients with	
	Single Attack	Multiple Attacks
<1 year	73	7
1–	3	42
5–	2	28
10–	2	12
15–	1	10
20–	—	4
25+	—	1
Total	81	104



30 cases of Reiter's syndrome followed for 10 years or more from the onset, showing recurrences of arthritis (26 cases) and the influence of fresh urethral infections on the course of the illness.

In all, 30 patients could be followed for 10 years or more from the onset of their illness, and, although attempts have been made to see as many patients as possible over a prolonged period, it is certain that this group is not representative of the whole series but is biased in containing the more seriously and chronically involved cases. Nevertheless, the study of these patients proved especially rewarding, as it demonstrated several interesting features (see Diagram). It can be seen that reinfection with venereal urethritis, be it gonococcal or non-gonococcal in nature, did not inevitably lead to further arthritic attacks. There was, in fact, no obvious reason why some episodes of urethritis in the same patient were followed by arthritis and others were not. No clinical difference in the character of the urethritis was found. The Diagram shows also that some later attacks of arthritis were not always preceded by urethral infection, unlike the first attacks in this group. Another interesting observation brought out by this long-term study is the extreme variability of the intervals between attacks; these were as short as three months or as long as 18 years.

Multiple Attacks

More than one attack of arthritis occurred in 104 patients. A total of 304 attacks were recorded in this group, the frequency distribution of which is shown in Table VIII.

TABLE VIII.—*Frequency Distribution of Multiple Attacks in 104 Cases with Reiter's Syndrome*

No. of Attacks	No. of Cases	No. of Attacks	No. of Cases
2	54	6	1
3	24	7	1
4	14	8	1
5	8	9	1
		Mean:	2·9 attacks

Forty-eight patients claimed that one or more of the later episodes were "unprovoked," as there had been no sexual intercourse during the preceding two to three months. In 22 of these attacks urethritis was absent, and in a further two instances non-specific urethritis appeared only *after* the onset of arthritis. On assessment, most of these attacks were considered to be relapses. Apart from the notable absence of urethritis in some of these cases, there was an unusually high incidence of iritis and sacroiliitis. In the whole series there were 21 cases with iritis, and 17 of these occurred in patients with probable relapses; of the total of 16 cases with sacroiliitis, 9 were found in this selected group. In contrast, rather more patients had subsequent attacks following the pattern of their first one—that is, sexual intercourse—urethritis—joint and other changes. A few cases showed both types of attacks at different times. Apart from the difficult problem of relapse *versus* reinfection, it was noted that with repeated attacks recovery became less complete.

Precipitating Factors

A careful search was made for precipitating factors other than urethral infection. None were identified with certainty, but some experiences are worth recording. In four patients with previous Reiter's syndrome, diarrhoea occurred as a result of food-poisoning (2 cases) and antibiotic therapy for an unrelated condition (2 cases), and was followed within one to five days by a new attack of arthritis. This is of interest because of the known association of a similar syndrome with acute dysentery. In three patients second attacks of the full syndrome followed within two to seven days after urogenital surgery or instrumentation (hydrocele operation, dilatation of a urethral stricture, and salpingectomy for chronic non-specific salpingitis). In six cases one

attack was preceded by tonsillitis. In all these instances the first attack followed venereal urethritis, and the possibility of the above conditions being associated by chance only with the later episodes cannot be ruled out.

Predisposing Factors

In the last 109 cases systematic inquiry regarding "rheumatic diseases" in parents, siblings, and offspring was undertaken; of these, 14 (12.9%) gave a clear account of rheumatoid arthritis in their families, compared with 9 (2.2%) in a control group of 400 cases attending with uncomplicated N.S.U. or gonorrhoea (Boyd, Oates, and Csonka, 1958). These findings suggest that there may be a hereditary predisposition to the arthritic manifestations of Reiter's syndrome.

There was only one known instance of Reiter's syndrome occurring in more than one member of a family in the entire series. It concerned two brothers who lived in different parts of England and who developed severe attacks within three months of each other. A common sexual source was denied.

Once a patient has suffered from this syndrome it seems likely that sooner or later the condition will recur. It is open to question whether this is due to a change brought about by the first attack or whether the increased susceptibility is inherent in the patient. A similar problem presents itself in rheumatic fever, in which both predisposition and infection with a specific organism play their part and where the prevention or early treatment of haemolytic streptococcal infection is successful in stopping further attacks. Whether a similar policy would be as beneficial in the management of patients with a history of previous attacks of Reiter's syndrome has not yet been adequately explored.

Dissociation of Symptoms

Many patients showed a rapid evolution of the classical features of the syndrome in a matter of days or weeks, as described in the literature, but some differed by a marked dissociation in the time of appearance of the cardinal symptoms—for example, one patient presented himself with non-specific urethritis and arthritis; nine years later he was seen with another similar attack, but with additional conjunctivitis for the first time. Another patient had recurrent episodes of urethritis and circinate balanitis over a period of two years; at the end of this time he developed severe arthritis and conjunctivitis. Yet another had urethritis and arthritis on three occasions; and on the fourth, nine years after the first attack, he developed iritis as well, which became the dominant feature of his recurrent active phases. In general, iritis was especially prone to make a late appearance, and keratodermia blennorrhagica was also a late-comer on occasion. The record in this series is held to date by a man whose first attack of urethritis and arthritis was followed by a symptom-free interval of 18 years, when he contracted venereal urethritis once more, and this was associated with arthritis and also conjunctivitis. These experiences lend support to the view that the various components of the disease need not occur simultaneously and that the "incomplete" syndrome is essentially of the same nature as the more fully developed one. This last point was probably demonstrated by two of our patients who gave the same female contact as source of their urethritis; this was followed in the one case by arthritis only and in the other by the full triad.

Sequelae

No deaths were attributed to the syndrome. The long observation period allowed a study of the late changes, and the more important of these are summarized in Table IX. Most of the patients with recurrent iritis had also one or more of the other listed sequelae, such as foot deformities or sacroiliitis, and the total number of individuals with some measure of permanent damage was 28. In addition to this group with well-defined changes there were a further six patients who were handicapped by a mild-to-moderate activity in various joints for periods of two to three years but who have not shown residual joint damage so far.

TABLE IX.—*Sequelae*

	No. of Cases	Remarks
Recurrent iritis	21	In 8 cases this became the dominant feature of the illness, with some visual loss
Foot deformities (pes valgus, pes cavus, subluxation of toes, periostitis of heels)	23	
Ankylosis of peripheral joints	8	The joints involved were: toes (4), hip (2), knees (2), elbow (1), tarsal joints (1)
Sacroiliitis	16	One patient showed also spinal involvement; the rest were limited to the sacroiliac joints

Summary

This paper records 185 patients with arthritis following genital infection, mostly venereal urethritis, who attended St. Mary's Hospital, London, over the past 15 years.

There were 182 males and 3 females in this consecutive series; 87 cases had arthritis only and 98 showed additional features, especially eye and skin involvement.

More than one attack occurred in 104 patients, and some of the later episodes appeared to arise independently of sexual contacts and may have been relapses.

The follow-up period in 30 cases extended for 10 years or more. Not every fresh urethral infection led to further attacks of arthritis. The intervals between attacks varied from a few months to 18 years. Possible predisposing and precipitating factors are discussed.

A dissociation of symptoms was noted in some cases when eye or skin lesions were not seen until years after the first attack. This suggests that the initial "incomplete" form of the syndrome is essentially of the same nature as the fully developed one.

Sequelae included sacroiliitis, deformed and chronically painful feet, ankyloses of peripheral joints, and visual disturbances resulting from recurrent iritis.

This work was carried out under the aegis of the Medical Research Council Working Party on Non-Specific Urethritis, with the aid of a grant from the U.S. Public Health Service. I thank Dr. G. L. M. McElligott for his permission to investigate the cases under his care and for his invaluable help, and Mr. A. J. King, of the London Hospital, for his interest and advice.

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The Marie Curie Memorial Foundation has prepared twelve pamphlets with the object of informing the general public about cancer. They are titled respectively: (1) "What is Cancer?", (2) "Some Facts about Cancer for Women," (3) "Some Facts about Cancer for Men," (4) "Cancer of the Skin," (5) "Cancer of the Mouth," (6) "Cancer of the Breast," (7) "Cancer of the Digestive Organs," (8) "Cancer of the Womb," (9) "Cancer of the Urinary Organs," (10) "Cancer of the Respiratory Organs," (11) "The Prevention of Cancer," (12) "The General Care of the Patient with Cancer." Copies of these pamphlets may be obtained (price 2d. each, postage 1½d.) from the secretary of the Foundation, 124, Sloane Street, London, S.W.1. The Foundation's chairman is Lord KERSHAW, and the vice-chairman Mr. RONALD W. RAVEN, F.R.C.S.

SENSITIVITY OF STRAINS OF GONOCOCCI TO PENICILLIN, SULPHATHIAZOLE, AND STREPTOMYCIN

BY

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Sulphonamides provided the first effective treatment for gonorrhoea. In a short time, however, strains of gonococci appeared which were resistant to sulphonamides, and by 1949 Dunlop was able to report that 86% of patients seen at the London Lock Hospital in 1946–7 were resistant to treatment.

Sulphonamides have now been replaced by penicillin and a careful watch has been kept for the appearance of penicillin-resistant gonococci. Such strains can readily be formed in the laboratory by exposure of the organisms to the drug, and it is perhaps surprising that until very recently there has been no evidence that resistant strains have been produced under natural conditions. In this paper we report the sensitivity of strains of gonococci from 200 patients to penicillin, streptomycin, and sulphathiazole. We have observed the relation between the patient's clinical course and the *in vitro* sensitivity results.

Patients.—Between October, 1957, and February, 1958, cultures were obtained from all male patients with gonorrhoea attending the venereal disease departments at St. Thomas's and St. Bartholomew's Hospital. Cultures were also collected from the female contacts when they attended. Satisfactory cultures for sensitivity-testing were obtained from 200 of 295 patients; in addition, a further 11 cultures were obtained from 10 of these 200 patients in whom the gonorrhoea recurred. Of these 200 patients, 190 were males and 10 were females: four of the female patients' contacts were among the 190 males.

Methods of Isolation and Testing Sensitivity

Material from patients was collected with charcoal-tipped swabs which were stored in Stuart's medium at 4° C. In our hands batches of Stuart's medium varied in their ability to preserve gonococci. Primary cultures were usually made within four days, and for these and for sensitivity tests chocolate agar plates containing 10% horse blood were used. In preparation this medium was heated to 75° C., but not above, for 10 minutes, and then cooled to 50° C., in order to minimize the effects of sulphonamide-inhibitors in the agar.

The cultures were incubated in an airtight jar for two days at 37° C.; carbon dioxide was provided by placing a lighted night-light in the jar immediately before sealing.

Dilution sensitivity tests were done for the three drugs tested. Stock solutions of the antibiotics were kept at 4° C. The penicillin solution was renewed at least every two weeks, and the streptomycin solution every month. For determining sensitivities, serial dilutions of each of the three drugs in chocolate agar were prepared in Petri dishes immediately before use, and a "control" plate containing no drug was prepared at the same time. The plates were divided into numbered sectors so that batches of up to 12 strains of gonococci could be tested on one set of plates. For some strains the primary cultures could be used to provide the inoculum, but for others subcultures had to be used. In each case one to six colonies were suspended in approximately 0.2 ml. of broth, and one 1-mm. loopful of this suspension was used as the inoculum. The plates were incubated at 37° C. in candle-jars for 48 hours, and the end-points, regarded as the minimum concentration of drug necessary to prevent visible growth, were determined by inspection. As a check of the accuracy of the method the Oxford staphylococcus was inoculated on the penicillin plates on six separate occasions. This organism was inhibited by 0.032 unit/ml. once, and by 0.016 unit/ml. five times.

The nature and purity of the growth were checked for each organism by making films from the first plate which just permitted visible growth. Sugar fermentation was tested for each organism which needed more than 0.064 unit of penicillin per ml. for inhibition. All such organisms were found to have the reaction of *Neisseria gonorrhoeae*, except for one which was discarded from the series. The general sensitivity of the strains to sulphathiazole suggests that sulphonamide inhibitors were not seriously influencing the results.

Laboratory Findings

The main results are shown in Table I. For penicillin, 162 strains tested were inhibited by 0.064 unit per ml., but 16 strains needed 0.256 unit and 5 needed 0.512 unit per ml.

TABLE I.—*Sensitivity of Strains of N. gonorrhoeae from 200 Patients to Penicillin, Streptomycin, and Sulphathiazole*

Penicillin		Streptomycin		Sulphathiazole	
Minimum Inhibitory Concentration (unit/ml.)	No. of Strains Inhibited	Minimum Inhibitory Concentrations (μg./ml.)	No. of Strains Inhibited	Minimum Inhibitory Concentration (mg./100 ml.)	No. of Strains Inhibited
0·008	10	0·25	6	0·03	6
0·016	94	1	13	0·125	30
0·032	46	4	139	0·5	82
0·064	12	16	42	2	69
0·128	17			8	12
0·256	16			>8	1
0·512	5				

For streptomycin, 158 of the strains were inhibited by 4 μg./ml. and all by 16 μg./ml. To our surprise 199 of the 200 strains were inhibited by 8 mg. or less of sulphathiazole per 100 ml.

Clinical Findings

At both hospitals the routine treatment for gonorrhoea was a single intramuscular dose of 300,000 units of procaine penicillin, and this was given to 190 of the patients. Following treatment the gonorrhoea recurred in 25 patients; all had received the standard dose except one who had been given 600,000 units. In attempting to correlate therapeutic results with the laboratory sensitivity tests it was decided on arbitrary grounds to consider strains needing 0.128 unit or more of penicillin per ml. for inhibition as possibly resistant. There were 38 patients with such strains, and analysis showed that gonorrhoea had recurred in 13. Three of these admitted further intercourse and may have been reinfected. Of the remainder, 2 defaulted immediately after treatment, and the remaining 23 had no observed recurrence in a follow-up ranging from one day to three months.

Among the 162 patients infected with sensitive strains there were 12 in whom a recurrence was observed: five of these admitted further intercourse and may have been re-infected. Ten patients defaulted after treatment, while there was no recurrence of gonorrhoea in 140 patients with a follow-up again ranging from one day to three months.

Further sensitivity tests were obtained in 10 of the 25 patients in whom the gonorrhoea recurred. In two patients, thought to be reinfected from the original source, both strains of gonococci were "sensitive." In seven patients, at

TABLE II.—*Clinical Course of 10 Patients with Repeated Sensitivity Tests*

Patient:	1	2	3	4	5	6	7	8	9	10
1st Attendance:										
Gonococci	+	+	+	+	+	+	+	+	+	+
Penicillin sensitivity (unit/ml.)	0·128	0·256	0·256	0·032	0·016	0·256	—	0·256	0·256	0·256
Procaine penicillin (100,000 units)	3	3	3	3	3	3	3	3	3	3
1st Failure:										
Gonococci	+	+	+	+[3]	+[3]	+	+	+	+	+
Penicillin sensitivity (unit/ml.)	0·512	0·512	0·512	0·016	0·016	—	—	0·128	0·128	0·256
Procaine penicillin (100,000 units)	6	6	6	3	3	6	6	6	6	6
2nd Failure:										
Gonococci	+	—	—	—	—	+[4]	+	—	—	+
Penicillin sensitivity (unit/ml.)	0·512					0·016	0·256			—
Streptomycin (g.)	1					1	1			1
3rd Failure:										
Gonococci	—					—	+[3]			+
Penicillin sensitivity (unit/ml.)							0·512			—
Streptomycin (g.)							1			2
Gonococci							—			—

[1] = 1,200,000 units procaine penicillin. [2] = 2,400,000 units procaine penicillin. [3] = Admitted further intercourse with original contact. [4] = Possible intercourse with fresh contact.

least six of whom were thought to be suffering from a relapse rather than reinfection, the original "resistant" strain was recovered from the second specimen. In one patient the original resistant strain was replaced by a sensitive strain, but this patient was known to have at least two homosexual contacts. The results of treatment in these patients are shown in Table II.

Of the female patients who had male contacts in the series, three of the pairs each had sensitive strains: the remaining pair were each infected by resistant gonococci.

Of the 200 patients, 127 were of European or Asiatic racial origin, the remaining 73 being of the negro race. Twenty-three of the "resistant" strains were isolated from the first group and 15 from the second.

Discussion

During the period in which gonorrhoea was treated with sulphonamides the number of clinically resistant cases progressively increased. This increase was associated with a rise in the numbers of *in vitro* sulphonamide-resistant gonococci. Lankford, Scott, and Cooke (1943) reported that all of 100 strains were inhibited by 5 mg. of sulphathiazole per 100 ml., whereas by 1949 Love and Finland (1955) found that the majority of 63 strains needed more than 40 mg. of sulphadiazine per 100 ml. When penicillin replaced sulphonamides in the treatment of gonorrhoea the proportion of sensitive strains began to increase, and by 1954 Love and Finland found that 73% of 43 strains could be inhibited by 2.5 mg. of sulphadiazine per 100 ml., although there were still some strains which required more than 40 mg./100 ml. Our findings presumably reflect the abandonment of sulphonamides for the treatment of gonorrhoea in this country in recent years.

Penicillin produced a welcome improvement in treatment, but the fear remained that gonococci resistant to penicillin might emerge. Until very recently there has been no confirmed evidence that this has happened. Penicillin is effective so rapidly that it might be difficult to distinguish relapse from reinfection, and it is probable that some apparently clinically resistant cases can be accounted for in this way. This was the view of Cohn and Seijo (1944), who investigated 35 supposedly penicillin-resistant cases and successfully treated 34 with penicillin alone. They were supported by Hughes and Carpenter (1948), who examined 216 cases of alleged penicillin-resistant gonorrhoea. Gonococci could be found in only 19 of these cases, and these were all cured with one or two doses of penicillin in oil and beeswax.

There has also so far been no evidence from sensitivity tests that penicillin-resistant strains have been emerging. Six papers have reported the sensitivity of 1,012 strains of gonococci between 1944 and 1954 (Cohn and Seijo, 1944; Lankford, 1945; Kenedy and Alföldy, 1947; Hawks and Greey, 1948; Cohn *et al.*, 1949; Love and Finland, 1955). Of all these strains, only five have been reported as requiring more than 0.128 unit of penicillin per ml. for inhibition, and three of these five may have in fact have needed less, as the immediate lower inhibitory levels were not tested.

In contrast to these findings, we found that 38 of our strains from 200 patients required 0.128 unit or more per ml. of penicillin for inhibition and five needed 0.512 unit. The clinical course of patients infected with these strains suggested that the increased *in vitro* resistance to penicillin might be reflected in the results of treatment with conventional doses of penicillin. Ignoring the possibility of reinfection, 13 of the 38 patients (34%) infected with resistant strains relapsed, as opposed to only 12 of the 162 patients (7%) who were infected with sensitive strains. That resistance was constant for at any rate a short period was indicated by the few results in which relapses occurred with the original infecting strain, and by strains of similar resistance which were isolated from infected partners.

The overall cure rate, using 300,000 units of procaine penicillin, is not unsatisfactory (87.5%), but in view of the experience described in this paper a dosage of 600,000 units will be used in future, and clinical relapse will be treated with streptomycin and sulphonamides.

Summary

The sensitivity of strains of gonococci from 200 patients has been tested to penicillin, streptomycin, and sulphathiazole. 158 of the strains were inhibited by 4 μg. of streptomycin per ml. and all by 16 μg./ml. Only one strain needed more than 8 mg. of sulphathiazole per 100 ml. for inhibition. Thirty-eight strains needed 0.128 unit or more of penicillin per ml. for inhibition, and patients infected with these strains relapsed after treatment more often than those infected with more sensitive strains (34% to 7%).

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The *Medical Directory* for 1958, the 114th annual issue, is now available from Messrs. J. & A. Churchill, Ltd., 104, Gloucester Place, London, W.1 (2 parts, 84s.). It contains 89,468 entries, over 2,000 more than last year.

FORCED EXPIRATORY VOLUME AS A TEST FOR SUCCESSFUL TREATMENT OF ASTHMA

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This paper describes a method of interpreting measurements of "forced expiratory volume" so that they can be used not only as a quantitative measure of change in asthma but also to determine when maximum benefit from treatment is obtained and whether the patient is likely to have underlying emphysema.

Forced Expiratory Volume

Definitions and Terminology

In asthma the maximum amount of air that a patient can breathe per minute ("maximum breathing capacity," or M.B.C.) is reduced. The severity of asthma is often assessed by measuring the vital capacity (V.C.), but this is unsatisfactory because the defect in asthma is mainly obstruction to air flow rather than restriction of chest movement, as in pulmonary fibrosis, etc. Thus a patient with asthma may have an almost normal V.C. if the exhalation is made very slowly, yet be able to exhale very little air quickly. It is therefore not surprising that measurement of the volume of air which can be exhaled in a given time (usually either three-quarters or one second) during a rapid and forced expiration following a maximum inspiration—in other words during a "forced vital capacity" (F.V.C.)—has been found to be more closely related to the M.B.C. than is the V.C. (Tiffeneau *et al.*, 1949; Kadlec and Vyskocil, 1950; Gaensler, 1951a; Kennedy, 1953). This volume will be called the "forced expiratory volume" (F.E.V.) qualified by the time in seconds over which it is measured.

There are a number of ways of measuring it in use. Usually the measurement is from the start of the F.V.C., and this is implied unless otherwise specified. Thus, when the time interval is 0.75 or 1 second, the abbreviations F.E.V.$_{0.75}$ and F.E.V.$_1$ are used. The volume exhaled over a second, after 0.25 second has elapsed from the start of the F.V.C., would be the F.E.V. 0.25–1.25. This terminology, recently recommended for general use by the Thoracic Society (Gandevia and Hugh-Jones, 1957), avoids the specific terms which have been applied to the measurement taken over the different time intervals; the differences between them are of little significance for most clinical purposes, and the different terms are becoming confusing.

Apparatus and Methods

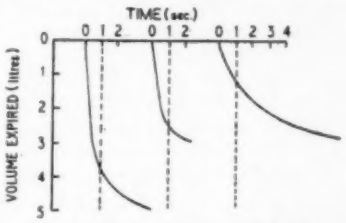
Recording the F.E.V. is far less tiring for the patient and simpler for the physician than measuring the M.B.C. directly by getting the patient to hyperventilate maximally and collecting the total amount of air exhaled over 15 seconds. The apparatus required is a simple spirometer with a light bell, similar to the type described by Bernstein *et al.* (1952), into which the patient delivers the F.V.C. through a mouthpiece or mask. The F.E.V. is measured either by taking a tracing (Fig. 1) on a fast kymograph of the movement of the spirometer bell during an F.V.C. test, from which the time and volume can be measured with a suitable scale, or by an automatic timing device (Gaensler, 1951b). The latter was used for the routine measurements presented in this paper, though in general we prefer a tracing, since it is hardly any more trouble and provides a permanent record with more information.

For clinical tests we record the F.E.V.$_1$ with the patient seated. After preliminary practice, the mean of three readings is taken. Perhaps rather surprisingly, the measurement is not very sensitive to the patient's co-operation (McDermott and McKerrow, 1956), provided a full inspiration is insisted on before the forced expiration. Thus the variation between the three readings is small.

Interpretation

The F.E.V. represents a reasonably fixed part of the cycle of breathing (D'Silva *et al.*, 1953) during maximum ventilation, and the M.B.C. can be predicted with great precision —r=0.9 approximately (Gaensler, 1951a; Kennedy, 1953)— by multiplying the F.E.V.$_{0.75}$ by a factor of 40 (Kennedy, 1953) or the F.E.V.$_1$ by a factor of 37 (Cara, 1953). For the F.E.V.$_1$ the simpler factor of 35 is commonly used, the resulting systematic error in the predicted M.B.C. being negligible.

This whole procedure of multiplying the result by a constant has no merit, and the values of the F.E.V. itself should be used. The only justification is that often the normal values for the M.B.C. are familiar, whereas those for the F.E.V. are not.



	A. Normal Subject	B. Ankylosing Spondylitis	C. Asthma & Emphysema
F.V.C. (litres)	4·90	2·90	2·90
F.E.V.$_1$ (litres)	3·90	2·60	1·20
Ind. M.B.C. (litres/min.)	136	91	42
F.E.V.$_1$ %	80	90	41

FIG. 1.—Tracings recorded when measuring the forced expiratory volume, showing comparison of the normal (A) with those from patients with purely "restrictive" (B) and mainly "obstructive" (C) chest lesions. (Note: As the spirometer rises during expiration the pen falls, so that the volume expired is traced downwards.)

The F.E.V.$_1$, like the V.C. and M.B.C., has a wide range of normal values depending on the age, sex, and size of the patient. However, expressed as a volume per second it is a measure of mean air flow, so the change in it in an individual is a simple measure of the effect of treatment in asthma, independent of the problem of its normal value.

Significance of the F.E.V.%

The F.E.V. is not only a simpler practical measure than a direct record of the M.B.C., it also provides more information. The F.V.C. is recorded at the same time, and the proportion of the latter that the F.E.V. represents (usually expressed as a percentage, and abbreviated here to "F.E.V. %") is held to be of diagnostic importance. In normal subjects the F.E.V.$_1$ is greater than 70% of the V.C. (Tiffeneau *et al.*, 1949; Gaensler, 1951a; Pemberton and Flanagan, 1956); in subjects with a purely restrictive defect of ventilation (as in ankylosing spondylitis, some cases of pulmonary fibrosis, etc.), both the F.E.V. and V.C. are reduced proportionately, so that the F.E.V. still forms more than 70% of the V.C. (Fig. 1); in subjects with obstruction to the air-flow, however, the F.E.V.% may fall to very low values, of the order of 30–50 (Gaensler, 1951a; Drutel and Dechoux, 1952).

When the obstruction to the air flow is wholly or partly reversible, as in asthma, it might be expected that the F.E.V.% would increase with administration of effective bronchodilator drugs, yet from a series of routine clinical tests the impression was gained that an increase in the F.E.V.% did not, in fact, occur in spite of an increase in the absolute value of the F.E.V.$_1$ and obvious clinical improvement. Below we present results which show this paradoxical lack of change in F.E.V.% during routine tests, and then some trials on individual patients which demonstrate the circumstances in which the F.E.V.% does change

towards the normal value and the significance of recording F.E.V.% for the assessment of the effectiveness of antispasmodic therapy and help in diagnosis.

Effect of Treatment on Change in the F.E.V. Relative to the V.C. in Asthma

Acute Response

The records were studied of 38 consecutive patients with severe asthma who had shown a definite response to a three-minute inhalation of a 1% isoprenaline aerosol, as shown by an increase of at least 10% in the absolute value of F.E.V.$_1$. There were 26 male and 12 female patients, their ages ranging from 13 to 72 years. On clinical grounds 25 of them had bronchitis or emphysema as well as asthma, the remainder being considered to simply be suffering from asthma with otherwise functionally normal lungs. On comparing the F.E.V.% before and after treatment (Fig. 2) the

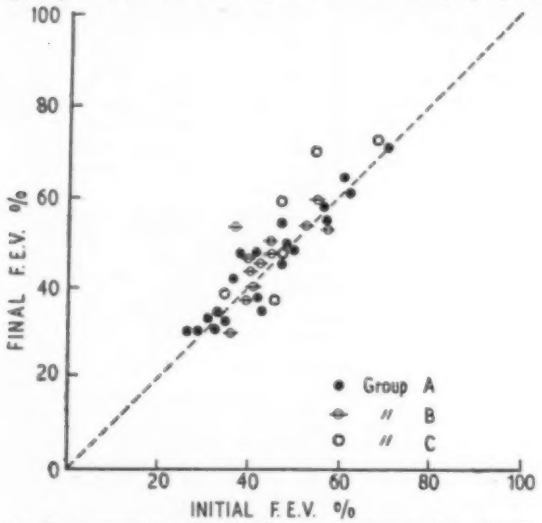


FIG. 2.—Comparison of the F.E.V., as a percentage of the F.V.C., before and after three minutes' inhalation of isoprenaline aerosol. Figures from 38 asthmatic patients who showed a definite response to this treatment in the increase in their absolute F.E.V.$_1$ of: group A, 10 to 25%; group B, 25 to 50%; group C, more than 50%.

results confirmed our impression that this percentage showed hardly any change, the points scattering closely to and on both sides of the 45-degree line, representing no change. Moreover, this lack of change seemed independent of the magnitude of change in the F.E.V. itself, as shown by the symbols representing grouped results in Fig. 1. In these patients the F.E.V. was expressed as a percentage of the F.V.C. rather than as a percentage of the V.C. measured from a full, unhurried, and steady expiration, which gives a more reliable reading, especially in asthma and emphysema (Gilson and Hugh-Jones, 1949; Scarrone *et al.*, 1955). However, subsequent records, in which both the F.V.C. and the V.C. were measured, showed that the use of the F.V.C. as a point of reference did not account for the results.

The failure to observe an appreciable increase in F.E.V.% results from proportional increases in both the F.E.V. and the F.V.C. so that the ratio between them remains constant. Although at low initial values of the F.E.V.$_1$ the response to the administration of a bronchodilator aerosol is known to be incomplete (Lowell and Schiller, 1953; Hume and Gandevia, 1957), the results were surprising to us, since it might be expected that if some of the obstruction to the airways was removed there would be a relatively greater increase in F.E.V. and thus a rise in F.E.V.% towards the normal value of more than 70%. Thus special studies of the serial changes in individual asthmatic patients were made to see in what circumstances the normal percentage could be obtained.

Serial Response

Two groups of patients were compared. In the first there were four patients (two female and 2 male, aged 24, 27, 31, and 57 years respectively) who were thought clinically to have uncomplicated bronchial asthma, without other structural damage in the lungs. In the second group there were three patients (males aged 37, 57, and 60 years) in whom asthma was thought, clinically, to complicate bronchitis and emphysema. All had been admitted to hospital with status asthmaticus, and the F.E.V.$_1$, F.V.C., and V.C. were measured on them, at first twice daily and later daily, both before and after three minutes' inhalation of isoprenaline aerosol, during their recovery. During this time they received other treatment such as antibiotics, steroids, long-acting antispasmodics, breathing exercises, etc., which was thought appropriate clinically.

An example from each group which is representative of the others in the group is shown in Fig. 3, where the absolute values for the F.E.V.$_1$ are plotted against the

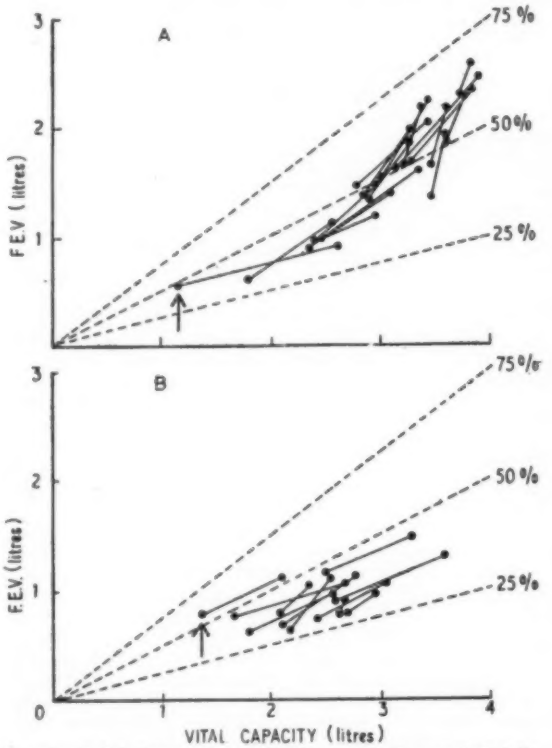


FIG. 3.—Serial changes in the F.E.V. and V.C. recorded daily during recovery from status asthmaticus, showing comparison of a case of "pure" asthma (A) with one where the asthma was a complication of severe emphysema (B). The arrows indicate the initial values on admission to hospital. ●——●=Change after three minutes' inhalation of isoprenaline aerosol.

V.C. The arrows indicate, in each case, the initial values obtained on admission to hospital when the patients had severe asthma and had low absolute values for F.E.V. and V.C. The values for the points before and after the aerosol are joined by lines whose length therefore indicates the extent of the acute response and whose slope indicates the change in the F.E.V. relative to the V.C.—that is, change in F.E.V.%.

It is apparent that there is always an incomplete response to single aerosol inhalation, a point emphasized by Lowell and Schiller (1953) and by Hume and Gandevia (1957). However, as the patient improves with treatment there is a difference in the response in the two groups of asthmatics. In each, both the F.E.V. and the V.C. initially increase proportionately, and where the asthma complicates emphysema

this proportionate increase continues until no further improvement in either is obtained and the F.E.V. as a percentage of the V.C. remains low. In the asthmatic patient whose lungs are otherwise normal, however, both the F.E.V. and the V.C. increase until the latter reaches a maximum value (which is presumably the normal for the patient), and the F.E.V.$_1$ continues to increase with further treatment and the lines of acute response to aerosol inhalation become steep, so that the F.E.V.% then, and only then, reaches its normal value of over 70%, when no further change takes place and treatment is complete. We have subsequently found this curvilinear response, obtained by serial readings of the F.E.V.% during treatment, to be typical of patients with uncomplicated asthma that we have investigated, and it is shown by two patients followed by Hume and Gandevia (1957) at the Brompton Hospital. It is not seen in patients whose asthma complicates emphysema; in them the F.E.V.% remains consistently low despite good response to treatment of their asthma, as shown by an increase in the absolute values of the F.E.V.$_1$ and V.C.

Discussion and Conclusions

Other workers (Dulfano *et al.*, 1953; Lowell and Schiller, 1953) have reported that at low initial values the F.E.V.% tends to remain constant after an inhalation of a bronchodilator aerosol. Dulfano *et al.* studied 36 patients with asthma and remarked that "the ratio of the first second to the total vital capacity" appeared to be remarkably constant for a given patient. They suggested that the constancy of the ratio might indicate a "fixed state" of the bronchial tree. However, they made single observations on patients rather than serial readings, and it is evident from our results that a low F.E.V.% which does not change after the single administration of a bronchodilator aerosol can either mean that the patient is an insufficiently treated asthmatic and that eventually the percentage will increase, or that he has permanent structural damage in the lungs, and then it will remain low in spite of any improvement shown by an increase in the absolute F.E.V.$_1$. Serial readings will help to decide between these alternatives if other lung-function tests are not available. The explanation for the finding of a constant F.E.V.% after a single administration of a bronchodilator aerosol in our patients (Fig. 1) is that these patients were all referred during an exacerbation of their disease, and had a low initial F.E.V. and F.E.V.%. Thus, whether they had underlying emphysema or were merely suffering a relapse of bronchial asthma, they were on that part of the curvilinear change in F.E.V.% shown in Fig. 3 where the F.E.V.% is low and does not change after the administration of bronchodilator spray.

Because of the limited nature of our investigations we do not offer any explanation for the curvilinear form of the change in F.E.V.% obtained in the cases of asthma, but the results are presented because we have found serial readings of the F.E.V., together with calculation of the F.E.V.%, to be of value in the practical treatment of patients with asthma, and we draw the following conclusions about them:

1. Serial recording of the F.E.V.$_1$ (or possibly some similar variation of it, easily got from the tracing, such as the mean mid-expiratory flow of Leuallen and Fowler (1955), etc.) is one of the simplest and most valid methods of assessment of treatment in asthma so far available. Changes in F.E.V. continue until asthma is removed, whereas the V.C. shows marked change only at the stage of moderate to severe disability with low initial values of the V.C.

2. Since the F.E.V.$_1$, like the V.C., has a wide range of normal values, even after allowing for the effects of age and sex, it is difficult to tell when an individual patient has reached his own normal value. Herein lies the particular value of calculating the F.E.V.%, since when this reaches its relatively narrow limit of normal—about 70–85% (Drutel and Dechoux, 1952; Pemberton and Flanagan, 1956)—one can then presume, provided the V.C. is within the normal range, that treatment is complete and the F.E.V. unlikely to show further change. It is important to note that the wheeze may have disappeared from an asthmatic patient examined at rest some time before this happens.

3. Failure of the serial value of the F.E.V.% to increase beyond about 50% on continued and intensive treatment is highly suggestive of a patient whose asthma is complicated by emphysema. We cannot agree with Cara and Sadoul (1953) that a low percentage (25 to 55%) is itself diagnostic of emphysema, taken on a single reading. Other more complex lung-function tests are necessary to distinguish between the two conditions. But where such tests are not available the finding of a persistently low F.E.V.% in spite of vigorous and continued treatment, and increase in the absolute values of the F.E.V. and V.C., is highly suggestive of underlying emphysema.

Summary

The volume of air that a normal subject can exhale in one second from the start of a rapid forced expiration, following a full inspiration (the one-second "forced expiratory volume" or "F.E.V.$_1$") is about 80% of his vital capacity (V.C.). A reduction in the percentage expired (F.E.V.%) implies obstruction to the airways, and is found in both asthma and emphysema.

Data on 38 consecutive patients with moderate to severe asthma who showed marked benefit from three minutes' inhalation of isoprenaline aerosol, as measured by the increase in the absolute value of their F.E.V.$_1$, demonstrate that in these circumstances there is no change in the percentage expired. This is because both the F.E.V. and the V.C. increase proportionately. However, repeated observations on six asthmatic and three emphysematous subjects during daily treatment showed that: (1) in asthma, the F.E.V.% tends to remain constant until the V.C. approaches what is presumably the normal value for the patient, and only then, when the F.E.V.$_1$ increases further on continued treatment, does the F.E.V.% reach its normal value of about 80%; and (2) in emphysema, this disproportionate increase in the F.E.V. does not occur, so that the F.E.V.% remains low despite continued treatment and initial benefit from an increase in the absolute F.E.V.$_1$.

Measurement of the F.E.V.% is a simple test for clinical use. A low value suggests that the patient either has insufficiently treated asthma or emphysema as well. Serial readings help to distinguish the two. If when the V.C. is within the normal range the F.E.V.% reaches its normal value no further benefit can be expected from treatment.

We are indebted to Dr. Bryan Gandevia, Wunderly Travelling Fellow of the Royal Australian College of Physicians, who not only suggested the method of presentation of the serial readings but kindly provided data he had collected with Dr. Hume at the Brompton Hospital, for comparison with ours; also to Dr. C. M. Fletcher for letting us include readings taken on some of his patients during their treatment, and to Miss Heather MacLeish, who recorded most of the routine readings initially analysed.

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MYOCARDIAL AND CEREBRAL INFARCTIONS AS POST-OPERATIVE COMPLICATIONS*

BY

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Many of the complications following surgery, previously critical, are now preventable or readily curable as a result of advances in anaesthesia, transfusion, fluid and electrolyte management, and control of infection. Particularly in the geriatric group, where advancing years no longer constitute a bar to major surgery, myocardial infarction and cerebrovascular accidents are too often the causes of post-operative death. These complications, occurring just when recovery after a technically successful operation seemed assured, are erroneously regarded as non-preventable by surgeons, and few recorded studies of surgical patients have been presented (Master *et al.*, 1938; Davis *et al.*, 1951; Wróblewski and LaDue, 1952; Wasserman *et al.*, 1955).

The present study was undertaken to determine the nature, timing, and pattern of the complications relative to the patient's pre-operative status, the magnitude of operative injury, and the stage of his post-operative response in which the complication occurred. As a result, it might be possible to identify predisposing factors, or at least predict those patients in whom such accidents are likely to occur as a part of their response, or failure to respond, to accidental or surgical trauma.

The series consists of 30 patients at Grady Memorial Hospital and the Veterans' Administration Hospital, Atlanta, during 1956–7, who suffered either a myocardial infarction or a cerebrovascular accident within a period of 30 days of operative or accidental trauma. The large number of geriatric patients, particularly in the charity hospital, contributed to the high incidence of such complications.

The criteria for the inclusion of a patient with a myocardial infarct consisted either of a diagnostic electrocardiographic record, confirmed by a gradual return towards normal, or a positive necropsy finding. Patients without these definite findings were excluded, for the clinical findings in post-operative myocardial infarction are often different from those in the "spontaneous" form of the disease (Menard and Hurxthal, 1931; Jacobs, 1951). Thus cardiac pain is less prominent in the post-operative period, as the patients are often either recovering from general anaesthesia or still under the influence of post-operative analgesics. Unexplained hypotension, tachycardia, arrhythmia, or pulmonary oedema require the electrocardiographic exclusion of myocardial infarction. Infarctions may sometimes go unrecognized; those of minor extent recovering without specific therapy, or coming to light only when a mural thrombus is detached to form a cerebral, peripheral, or pulmonary embolus.

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The criteria for the inclusion of a patient with a cerebrovascular accident were either unequivocal clinical findings, with definite neurological signs such as hemiparesis or hemiplegia, or changes in the brain at necropsy. Lumbar puncture occasionally and electroencephalography rarely were used as adjuncts to diagnosis.

Nineteen patients with myocardial infarcts and 11 with cerebrovascular accidents satisfied these criteria for inclusion.

Material

The average age of the patients with myocardial infarcts was 70 years, of those with cerebrovascular accidents 66 years. The range of ages was similar in both groups: 46–93 years for the cardiac group, 48–80 in the cerebrovascular group. The sex incidence was different in the two groups, being 5 males to 1 female among the cardiacs, 2:1 among the latter group. Of the 19 patients subsequently sustaining a myocardial infarction, 12 (63%) had pre-operative evidence, apart from arteriosclerosis and mild hypertension, of cardiac disability. It is striking that, of the seven whose pre-operative evaluation was negative, three showed evidence of old as well as recent infarction at necropsy, one of these having had a normal electrocardiogram. Of the eight patients with pre-operative electrocardiograms, only three showed an abnormality indicating ischaemia. Two of these three patients developed post-operative myocardial infarcts; the other had a cerebrovascular accident.

The patients with cerebral complications showed a rather similar picture. Pre-operatively, five (45%) had evidence of cardiovascular disease apart from mild hypertension. One of the six without pre-operative evidence of cardiovascular disease had clear evidence at necropsy of both old and recent areas of cerebral softening.

Hypertension (systolic pressure over 140 mm. Hg. or a diastolic pressure over 90 mm.) was present in 19 (63%) of the 30 patients.

In retrospect, two-thirds of these patients might have been expected, on estimation of their pre-operative cardiovascular status, to have a predilection for one of these complications. However, in attempting to make a total appraisal of each patient, taking into account not only his cardiovascular reserve but also the magnitude of the anticipated surgery, only 7 out of the 30 patients were classified as relatively "good risks" from the point of view of fitness for anaesthesia and surgery.

Operation and Injury

Among the patients who developed myocardial infarction the site of operation or trauma was the abdomen in 11 patients, the extremities in 5, and the chest in 3. In the cerebrovascular group the abdomen was the site in 6, the extremities in 2, the chest in 2, and the neck in 1. Thus operations on the abdomen preceded these complications in half of the patients. Those with cardiac or intracranial operations were excluded.

Nine of the myocardial infarcts were preceded by accidental trauma or emergency operations and 10 by elective procedures; five of the cerebral accidents were preceded by emergency and six by elective procedures. The complications, therefore, were equally divided between the urgent and elective operations or, stated differently, between the acute and chronic diseases.

The type of anaesthesia varied. The most striking feature in a detailed analysis of the agents used is that the complications followed the use of local analgesia in seven patients (23%). Of the 13 which followed general anaesthesia, relaxant agents were used in seven. Spinal anaesthesia was used in six patients, refrigeration in one, and no anaesthetic was given to three (two burns and one fractured humerus). The two complications showed approximately equal distribution of the various anaesthetic agents.

Shock and Hypotension

No patient was hypotensive pre-operatively. Nine (47%) of those with myocardial infarcts had a recognized period of hypotension during operation or anaesthesia, but in two of these the infarction was so closely related to the hypotensive episode that the latter might have been effect rather than cause. In several patients the sequence of events appeared clearly to indicate that the infarction occurred during a period of surgically induced hypotension, the hypotension causing the infarction. The following case-history is illustrative :

A 68-year-old man was assessed before resection of an aneurysm of the abdominal aorta. He was arteriosclerotic, with early fundal changes; his blood pressure was 165/90 and the pulses in his right lower extremity were diminished. He was anaesthetized with thiamylal sodium, nitrous oxide, oxygen, and suxamethonium chloride. The aneurysm was resected and a graft inserted without untoward effect. Removal of the aortic clamps produced a profound fall in blood pressure, which did not respond to adequate blood replacement and necessitated intravenous L-noradrenaline for the ensuing seven days. An electrocardiogram taken in the operating-room following the hypotensive episode revealed an acute myocardial infarction. He made a full recovery.

There was a period of hypotension during or after operation in seven (64%) of the patients who later had cerebrovascular accidents.

A known period of hypotension preceded at least one-third of the myocardial infarcts and two-thirds of the cerebrovascular accidents.

Time of Complication after Surgery.—The times of onset of the two complications showed a significant difference. Twelve of the 19 (63%) myocardial infarcts occurred on the day of operation or within the first three post-operative days; only 3 of the 11 (27%) cerebrovascular accidents did so, the remainder being spread over a period of the ensuing three post-operative weeks. Several of the latter accidents occurred at the beginning of the second week, the period often associated with a high incidence of thrombo-embolism in the venous system. In general, the patients in this series had cerebral accidents at any time throughout the first three weeks after operation or trauma, whereas myocardial infarction rarely occurred after the end of the first week.

Discussion

The finding that myocardial infarction occurred predominantly in older men agrees with findings in other series, apart from that of Wasserman *et al.* (1955), who had only 10 men in their group of 25 patients. The general incidence of myocardial infarction, unrelated to trauma, shows an average age of 62 years and a proportion of females varying from 7 to 17% (Bland and White, 1941). The various post-operative series show an average age of 62–69 years and the rather higher proportion of females of 16–60%.

Pre-operatively, two-thirds of the patients in this study had definite clinical manifestations of cardiovascular disease. The difficulties of adequate evaluation are apparent, however, from the presence at necropsy of old cerebral and myocardial infarcts which were unsuspected from the history, physical examination, and electrocardiogram. Master *et al.* (1938) found pre-operative evidence of cardiovascular disease in almost every one of his 35 patients.

The nature of the surgical procedure and the type of anaesthesia had little bearing on the incidence of complications. Apart from the dangers of hypotension in spinal anaesthesia (Davis *et al.*, 1951; Wasserman *et al.*, 1955) the lack of anaesthesia in three patients, local analgesia in seven, and refrigeration in one suggest that these complications do not result from the use of any specific anaesthetic agent. No known anaesthetic agent affects directly the oxygen-carrying capacity of the blood (Adriani, 1955).

The pathogenesis of myocardial infarction is obscure, but the actual lesion may take several forms. When the coronary arteries are already atherosclerotic a small thrombus may form on an atheromatous plaque or an intimal haematoma may occlude the lumen, infarction occurring if the patient survives long enough for the myocardial degeneration to follow. It is also now recognized that infarction may follow a period of diminished flow (coronary insufficiency), without demonstrable occlusion of the arterial lumen, when there has been a discrepancy between the demands of the myocardium and the available blood supply (Master *et al.*, 1947).

Such a discrepancy may follow an increase in the oxygen requirements of the myocardium as the cardiac work suddenly increases to meet the demands of an increase in blood pressure, cardiac rate, or cardiac output. This may result from severe physical exertion, emotional stress, tachycardia from any cause, or after the administration of such drugs as adrenaline. A similar discrepancy follows a sudden diminution in coronary flow as a result of hypotension, oligaemia, or extreme bradycardia. In a study (Vowles *et al.*, 1957) of coronary flow in dogs, coronary sinus flow was found to fall by 50% in acute haemorrhagic shock, despite a lowered coronary vascular resistance (Fig. 1). In

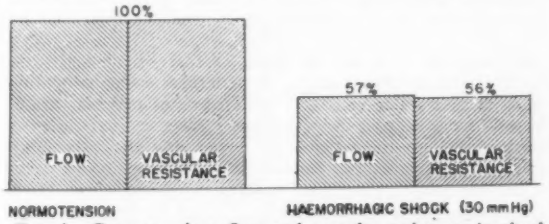

FIG. 1.—Coronary sinus flow and vascular resistance in shock (Vowles *et al.*, 1957).

the presence of coronary arteriosclerosis, vasodilatation may be so limited that haemorrhagic shock may result in an even more profound decrease in coronary flow. The haemodynamic law of Poiseuille, which states that if the pressure remains constant the flow in a tube varies as the fourth power of the diameter, emphasizes the great reduction in flow which occurs in a vessel narrowed by arteriosclerosis to half its normal diameter; if the systolic blood pressure falls only from 120 to 90 mm. the flow is $\frac{1}{16} \times \frac{3}{4}$—that is, under 5% of normal. A fall from 120 to 30 mm. reduces the flow in such a vessel to 2% of normal (Fig. 2).

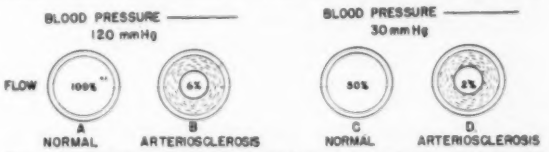

FIG. 2.—Diagrammatic representation of blood flow at normal blood pressure and in shock, in normal coronary vessels, and in vessels narrowed by arteriosclerosis to half their normal diameter. A, Normal flow. B, Flow=normal flow $\times \frac{1}{2^4}$=6%. C, Flow=normal flow $\times \frac{1}{4}$ (fall in pressure)$\times 2$ (diminished resistance)=50%. D, Flow=normal flow$\times \frac{1}{4} \times \frac{1}{2^4}$=2%.

In the current series a known period of hypotension preceded a significant number of the myocardial infarctions. Impairment of oxygenation of the coronary blood in anaemia or anoxia from respiratory depression or pulmonary dysfunction will result in a similar deficit. Many of these factors may be present in patients submitted to anaesthesia and major surgery, and in view of the large number with coronary artery disease it is surprising how few infarcts actually occur.

Phipps (1936), reviewing 437 cases of acute myocardial infarcts, found that 6% followed surgery, 13% followed a period of unusually severe exercise, 18% followed moderate or usual exercise, 51% occurred at rest, and 8% occurred during sleep. The high proportion of infarcts occurring in patients at rest was confirmed by Master *et al.* (1937), who found that 52% of 815 infarcts (in 555 patients) occurred

with the patient at rest. Master *et al.* pointed out, however, that these percentages correspond with the proportion of time spent in these various activities, and regarded them as insignificant. On the other hand, Fitzhugh and Hamilton (1933) found that in a high proportion of his patients the acute incident followed a period of unusual effort often accompanied by undue fatigue, inadequate sleep, and emotional strain. Some of these less easily assessable factors may well play a part in patients undergoing surgery. The occurrence of myocardial infarction following hypotension due to haemorrhage, "pleural shock," pulmonary embolism, or peritonitis has been described (Davis *et al.*, 1951).

Cerebrovascular "accidents" are usually classified into haemorrhage, embolism, thrombosis, and spasm. Hicks and Warren (1951), in a study of 100 necropsies of patients dying of these accidents, regard this classification as misleading. They believe that many of the haemorrhages demonstrated at necropsy are due to coalescence of minute petechiae into an infarcted and necrotic area, ischaemia being the underlying cause of all except the embolic lesion. In 60% of their necropsies showing infarction there was no vascular occlusion. They suggest that arterial spasm, which may respond to stellate ganglion block (Leriche and Fontaine, 1936) is the cause of hypertensive encephalopathy. Sodium and water retention, with cerebral oedema, small-vessel compression, and resultant ischaemia, may play a part similar to the mechanism underlying the encephalopathy which sometimes follows the administration of corticotrophin and cortisone (Josiah Macy Jr. Foundation, 1949).

In recent years the physiology of cerebral blood flow has been advanced by the nitrous-oxide desaturation technique of Kety and Schmidt (1948). Provided that the blood pressure remains above 60 mm. systolic, cerebral vasodilatation maintains adequate flow. Anoxia, carbon dioxide, ether, histamine, papaverine, and a local increase in metabolic needs due to cerebral activity are potent vasodilators. L-Noradrenaline is a cerebral vasoconstrictor in the normotensive patient, oxygenation being maintained by increased oxygen extraction. In the hypotensive patient noradrenaline still results in vasoconstriction, but the flow is so increased by the rise in pressure that oxygenation is improved. Anxiety and apprehension cause an increased oxygen consumption, but under general anaesthesia oxygen consumption is lowered to 40% of normal, normal flow being maintained (Kety and Schmidt, 1948; Kety, 1950).

In patients over 50, even though symptom-free, there is a reduction in cerebral blood flow and an increased vascular resistance compared with the younger age groups. These changes, which are even more marked in those with a history of cerebrovascular accident or evidence of arteriosclerotic psychosis, are not reversed by inhalation of oxygen, but are restored almost to normal by 5% carbon dioxide (Fazekas *et al.*, 1952; *Lancet*, 1954; Saunders, 1954).

Even without this apparent state of chronic spasm an acute form of cerebral vascular insufficiency may arise during hypotension from haemorrhage, coronary occlusion, spinal anaesthesia, or even sudden postural change. This generally transient and reversible insufficiency may produce irreversible damage to the brain. In monkeys, when one carotid or other large cerebral vessel has been experimentally occluded without detectable effect, induced hypotension then has a focal effect such as hemiplegia, from which the animal recovers if the hypotension is sufficiently transient. (Corday *et al.*, 1953).

Cerebrovascular accidents have been recorded after minor surgery, diagnostic procedures, and minimal accidental trauma, indicating that there are other more obscure factors of importance (Hammes, 1956).

It is apparent that several factors are common to the two post-operative complications. The hypertensive arteriosclerotic patient has a decrease in vascular adaptability with regard to these vital organs; an acute state of insufficiency occurs if there is a fall in pressure, a local increase in vascular resistance, diminished oxygen-carrying capacity of the blood, or an increased local metabolic demand. If the insufficiency is due to an actual vascular occlusion, ischaemia and infarction follow in heart muscle or brain. Even if the insufficiency is transient, irreversible changes may result. In this respect myocardial cells are less sensitive than cerebral cells; the latter can survive only four to five minutes of complete anoxia, those of the higher centres dying first. On the other hand, myocardial infarction may cause the immediate death of the patient, a sequence which rarely happens with cerebrovascular ischaemia.

Although the two complications have several antecedent factors in common, they present a striking difference in their time of occurrence, two-thirds of the myocardial infarctions being on the day of operation or the succeeding three days. Similar data are reported by other observers (see Table).

Time of Onset of Post-operative Myocardial Infarcts.

Author	Total No. of Patients	Percentage of Infarcts Occurring on Day of Operation and First Three Post-operative Days	Percentage of Infarcts Occurring During First Post-operative Week
*Davis *et al.* (1951) ..	18	83	89
Wróblewski and LaDue (1952)	15	60	66
Wasserman *et al.* (1955) ..	25	68	92
Master *et al.* (1938) ..	35	52	63
Current series ..	19	63	76
Total ..	112	65	77

* These patients are reported according to day of death.

The cerebral accidents were spread out over the first three post-operative weeks (Fig. 3). During and after trauma or operation, the factors operating to cause diminished oxygenation and hypotension are identical, but the metabolic demands of the heart and brain are not. Myocardial infarction is a result of a discrepancy between the needs and the available supply of oxygen to the myocardium. This discrepancy is most likely to arise during or immediately after the anaesthesia, and accidental or operative trauma; for at this time myocardial irritability is often increased, while tachycardia, hypotension, diminished venous return, peripheral circulatory changes, and alterations in depth and rate of respiration may all increase cardiac work and oxygen demands (Fig. 4). Once this period of maximal cardiovascular stress is over, it is unlikely to recur except as a result of a major mishap such as post-operative haemorrhage.

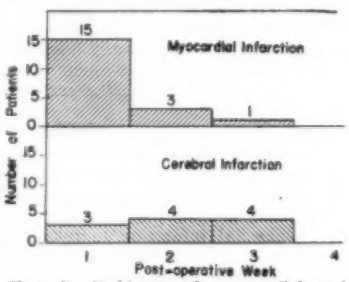

FIG. 3.—Incidence of myocardial and cerebral infarctions in successive post-operative weeks.

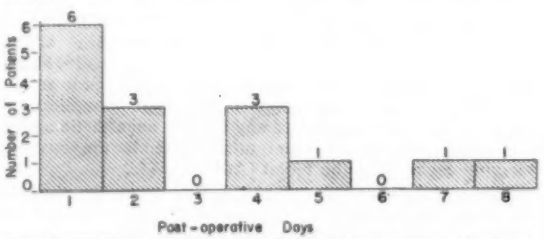

FIG. 4.—Incidence of myocardial infarctions on successive post-operative days.

Cerebral infarction is similarly due to a discrepancy between cerebral supply and demand for oxygen. Under adequate general anaesthesia, oxygen demands of the brain are so reduced (to less than half their normal value), that, unless gross anoxia such as that due to delay in treatment of cardiac arrest occurs, the oxygen supply is likely to be adequate. The brain is in a relatively protected state. Of the three patients in the current series whose cerebral infarcts occurred in the first week (on the day of operation and the first post-operative day), two had operations under local and one under spinal anaesthesia, so that this protection was lacking. Later in the post-operative course, continued narcotic administration, without the artificially augmented respiration of the operating-room, may cause respiratory depression and cerebral anoxia. Unfortunately it is the garrulous and wakeful patient with cerebral arteriosclerosis and a reversal of the normal sleep rhythm who is particularly likely to receive heavy nocturnal sedation. The high incidence of cerebrovascular accidents after cataract surgery and skeletal trauma is well known. The balance between the supply and demand of cerebral oxygen is so delicate that only a minor further mishap is needed to tip the scales. Anoxia follows, and need only be unrelieved for five minutes for the cerebral damage to be permanent.

Summary

A review of 30 patients who experienced cardiac or cerebral infarction during the 30 days following operation or accidental trauma suggests a biological difference between these two processes. Of the cardiac infarctions, 63% occurred during the operation or within the first three days after operation or injury. All but 23% occurred within the first week. To the contrary, the cerebrovascular accidents occurred without apparent predilection of time.

A period of hypotension was known to be associated with operation in 53% of the patients. Hypotension is known to result in a reduction in coronary flow. In the arteriosclerotic patient, whose coronary arteries are unable to dilate appreciably, the reduction in flow following hypotension is probably a major factor in the progression of ischaemia.

The complications could not be related to the anaesthetic agents used; indeed, eight followed the use of local analgesia. One patient received no anaesthesia (fractured humerus).

The increased oxygen requirements of the burdened heart, associated with the decreased coronary flow of hypotension, predispose it to an immediate oxygen deficiency. General anaesthesia reduces the oxygen demands of the brain so that an absolute oxygen deficit is as likely to be post-operative (atelectasis, narcotic respiratory depression, postural changes) as operative.

An urgent need is the rejection of the surgeon's concept that most of these complications are inevitable. Application and extension of the recognized principles of avoidance of anoxia, hypotension, and increased cardiac work in arteriosclerotic patients should prevent many of the myocardial infarctions. The biological and clinical factors underlying cerebrovascular accidents differ in not being specifically related to the period of trauma; attempted prevention necessitates the empirical application of such measures as adequate oxygenation, inhalation of carbon dioxide, and the avoidance of undue sedation in arteriosclerotic patients.

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TRENCH-FOOT IN PEACETIME ENGLAND

BY

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Severe injury from cold is seen in three main forms. Frostbite occurs if the temperature is low enough to cause actual freezing of tissues, while more prolonged exposure to a cold but non-freezing environment results in a trench-foot type of injury. Although this derives its name from its prevalence during the trench warfare of 1914–18, the occurrence of trench-foot among Napoleon's troops during the retreat from Moscow was described by Larrey (1812), and practically every military campaign fought in cold climates since that time has produced further cases. Similar to trench-foot in many respects is immersion foot, numerous examples of which were observed among shipwreck survivors in the 1939–45 war (Ungley and Blackwood, 1942; Webster, Woolhouse, and Johnston, 1942; White, 1943), while it has been suggested (Greene, 1941) that shelter foot is another type of local cold injury. It seems possible, however, that mechanical obstruction to the venous return, coupled with some deficiency of vitamin C, is more important than cold in the production of this last-named condition. Frostbite is a result of cold which may occur in time of war or peace (Brahdy, 1935; Kleitsch and Connors, 1954; Butler, 1957). Prolonged exposure to a low but non-freezing temperature is, however, very unlikely to occur under normal conditions of peace, and trench-foot is primarily a hazard of war.

The occurrence of two cases in peacetime England is rare enough to warrant this report. We have, in fact, been unable to find any record of similar cases occurring in this country, although the circumstances under which our patients sustained their injuries cannot be unique.

Case 1

A vagrant aged 54 first took to the roads in 1937. Apart from service with the Army from 1939 to 1945 he had had nothing but casual employment during that time, and had

been unemployed since December, 1955. During this most recent spell of unemployment he lived a precarious existence in the West End of London, and 16 days before admission he made his headquarters on a bombed site near Old Street Station. It was 10 weeks since he had taken off his shoes and socks, and while on the bombed site he became progressively less inclined to exert himself. Three days before admission his shoes fell apart and he remained relatively immobile. His feet were painful, but not excessively so. On March 20, 1956, he was too feeble to move, but his cries were heard by passers-by, and he was brought to St. Bartholomew's Hospital. Weather conditions during the period of exposure were average for the time of year. Recordings made at Regent's Park (see Table), which is approximately three miles (2.7 km.) from Old Street Station, showed a minimum temperature of 29° F. (−1.7° C.) on March 16 with a maximum of 59° F. (15° C.) two days later.

Weather Conditions at Regent's Park (Case 1) and at Sprowston (Case 2)

Regent's Park

	March, 1956							
	13	14	15	16	17	18	19	20
Maximum temperature of day (°F.)	39	46	40	48	57	59	54	57
Minimum temperature of day (°F.)	32	31	31	29	31	38	35	37
Relative humidity at 9 a.m. G.M.T. (%)	70	79	80	89	84	83	91	92
Rainfall for 24 hours ending at 9 a.m. next day (in.)	0·0	Trace	0·0	0·0	0·0	0·0	Trace	0·10
Mean wind speed for day (m.p.h.) (Kingsway)	8	7	5	3	3	8	9	9

Sprowston

	December, 1953							
	16	17	18	19	20	21	22	23
Maximum temperature of day (°F.)	50	49	47	48	46	45	50	47
Minimum temperature of day (°F.)	34	48	41	42	42	31	34	41
Relative humidity at 9 a.m. G.M.T. (%)	93	94	97	88	81	92	100	100
Rainfall for 24 hours ending at 9 a.m. next day (in.)	0·0	0·0	0·40	Trace	0·0	Trace	0·02	0·01
Wind at 9 a.m. (speed m.p.h.)	4–7	4–7	1–3	19–24	4–7	4–7	4–7	4–7
	Soft (muddy) wet ground							

On examination he was unkempt and bearded, but coherent and not complaining of pain. His nutrition was good and there was no obvious dehydration. The blood pressure was 80/60, pulse rate 100, pulse regular, temperature 100° F. (37.8° C.), and respirations 16. His pupils reacted to light and accommodation, the fundi were normal, and his tongue was furred. His hands were warm and showed no evidence of injury from cold, while the heart, lungs, and abdomen were healthy. His feet and lower legs (Fig. 1) were oedematous. The toes were cold and pale, the feet cold and cyanosed, while the ankles and lower legs were hyperaemic. Active movements of the feet and toes were possible, and the knee- and ankle-jerks were present and equal. All sensation below the ankles was lost. The femoral and popliteal pulses were strong, but the peripheral pulses were not felt, although oscillometry showed good arterial pulsation below the knees and above the ankles. The neurological system was normal, apart from the sensory changes in the legs.

FIG. 1.—Case 1, on admission.

Investigations.—Examination of the blood showed: Hb, 70% (Haldane); white cells, 10,000/c.mm. (polymorphs 82%, lymphocytes 12%, monocytes 6%); E.S.R., 25 mm. in the first hour (Westergren); W.R. and Kahn, negative; plasma protein, albumin 3.7 g./100 ml., globulin 2.8 g./100 ml. *X*-ray examination of the chest showed nothing abnormal, while that of the legs gave no evidence of arterial calcification. The urine had a specific gravity of 1020 and contained no albumin or sugar.

Treatment and Progress.—He was put to bed at normal room temperature with the feet elevated and exposed to the air. His general condition rapidly improved on a normal diet and fluid intake, his blood pressure rising to 120/80, but an intermittent pyrexia continued and transient albuminuria occurred 24 hours after admission. He was given 2 pints (1,140 ml.) of fresh blood, A.T.S., and penicillin, while a course of anticoagulant therapy was begun with phenindione ("dindevan"). On the day after admission a right temporary lumbar sympathetic block was performed with no noticeable effect, and thereafter he was given brandy, 1 oz. (28 ml.) twelve-hourly. After one week the swelling had largely subsided and the toes were becoming black. The distal parts of the feet were mauve, the proximal regions red, and large blisters had appeared. At this stage 10 ml. of 5% fluorescein was given intravenously and the feet were viewed under ultra-violet light. Fluorescence was observed throughout the feet and toes, although less well marked in the blackened areas, indicating that a good circulation was still in being. Five weeks after admission the skin over the feet, proximally, was blackened, while the gangrene affecting the toes was spreading proximally. The fluorescein test was repeated and good fluorescence was again observed in the feet distally and the toes. Despite this apparently favourable prognostic sign the general trend was gradually downhill. Although sensory perception spread to below the ankle and some new skin grew slowly downwards, the gangrene became more extensive (Fig. 2), until 12 weeks after admission bilateral below-knee amputations were performed.

FIG. 2.—Case 1, twelve weeks after admission.

Case 2

A Norwich youth aged 20 arrived home late on the evening of December 16, 1953, to find the doors locked and his parents in bed. Rather than risk their anger by awakening them he repaired to Mousehold Heath and slept under a bush. There he apparently remained for seven days, until December 23, when his cries attracted the attention of a passer-by and he was taken to the Norfolk and Norwich Hospital. Apart from some evidence of recent psychological maladjustment there was no relevant past or family history.

Weather conditions at the time of exposure were mild for the time of year. Recordings made at Sprowston (see Table), 1½ miles (1.4 km.) from where the boy was lying, showed a minimum temperature of 31° F. (−0.6° C.) on December 21 and a maximum temperature of 50° F. (10° C.) on the following day.

On examination he was conscious and coherent, but shocked, dehydrated, and very dirty. His pulse rate was 120, pulse regular, temperature 95° F. (35° C.), respirations 20, while the blood pressure was unrecordable. His eyes were sunken, but his pupils reacted to light and accommodation and the fundi were normal. His tongue was furred and there was surgical emphysema over the left pectoral and axillary regions, but the heart, lungs, and abdomen were otherwise normal. His hands were cold but showed no evidence of injury through cold. His feet and lower legs were grossly oedematous and cold, showing a blotchy cyanosis intermingled with areas of erythema and pallor. He was unable to move his feet, the ankle-jerks were unobtainable, while sensory perception below the knees was absent. The femoral pulses were palpable, but the more peripheral pulses could not be felt. There were no neurological abnormalities apart from those found in the legs.

Investigations.—Hb, 125% (Haldane); blood urea, 240 mg./100 ml.; plasma albumin, 5 g./100 ml., globulin 2 g./100 ml. The serum sodium, potassium, and chloride were normal. *X*-ray examination of the chest confirmed the presence of surgical emphysema and also revealed a small left pneumothorax. The urine was sterile and contained a small amount of protein, while microscopically it was normal.

Treatment and Progress.—He was put at rest in bed with the feet exposed, no excessive warmth being applied to the body or feet. A.T.S. and penicillin were administered, and during the first 12 hours he received intravenously 2 pints (1,140 ml.) of plasma and 3 litres of glucose–saline. As a result his general condition rapidly improved, the B.P. rising to 120/70. During the next two weeks this general improvement was maintained. The surgical emphysema disappeared, but his urine continued to be of low specific gravity and contained albumin. The blood urea rose initially to 300 mg./100 ml., but returned to the normal level of

FIG. 3.—Case 2, four weeks after admission.

40 mg./100 ml. 15 days after admission. Although the feet had become grossly blistered they also improved remarkably. They became hyperaemic and warm, and movement and some sensory perception returned. Four weeks after admission, however, areas of superficial gangrene had appeared (Fig. 3) and by April, 1954, the patient was emaciated and toxic, with bilateral infected gangrene. Local excision with skin grafting produced some temporary benefit, but gradual progression of the gangrene occurred and bilateral below-knee amputations were performed on July 1.

Discussion

Exposure to cold is, of course, necessary for the production of local cold injury, but constrictive clothing, immobility, wind-blast, damp, lowered body temperature, malnutrition, shock, and wounds may all be contributory factors. The means whereby tissue damage is produced is disputed, and while vasoconstriction, oedema (Greene, 1943), and intravascular sludging of red blood cells leading to thrombosis (Lange *et al.*, 1947) have been put forward as possible mechanisms, the balance of recent experimental evidence (Lewis, 1951, 1955) suggests that the direct noxious effect of cold on the tissues is the most important factor. The clinical picture is classically divided into pre-hyperaemic, hyperaemic, and post-hyperaemic stages, and there may be no qualitative difference between the symptoms of frostbite and those of trench or immersion foot (Lewis and Moen, 1952). The systemic sequelae are few, but renal damage has been reported both in the human (Laufman, 1951) and in the experimental animal (Lewis and Thompson, 1951). Case 2 showed evidence of gross renal impairment, but whether this was the result of shock or cold injury or a combination of both it is not possible to say.

Three main lines of early treatment have been advocated. In the experimental (Kreyberg, 1948) and clinical (Isaacson and Harrell, 1953) fields sympathectomy has proved of little benefit, possibly because sympathetic paralysis is already present in the cold injured part (Webster *et al.*, 1942), and the failure of a sympathetic block to produce any demonstrable effect in Case 1 was not unexpected. Although Lange and Loewe (1946) and Lange *et al.* (1947) are keen advocates of anticoagulant therapy, their enthusiasm is not shared by Fuhrman and Crismon (1947) or Pichotka and Lewis (1949), while their results are frankly doubted by Lewis and Moen (1953). On the basis that anticoagulants might prevent the effects of secondary thrombosis and at all events would do no harm, such treatment was employed in Case 1.

The only form of therapy which has been uniformly beneficial in experimental studies is rapid thawing (Fuhrman and Crismon, 1947; Lempke and Shumacker, 1951; Pichotka and Lewis, 1951), while Adams-Ray and Falconer (1951) obtained some confirmation of these findings in humans. Overheating (above 37.5° C.) must, of course, be avoided, and if the results of animal experiments are applicable to man (Entin and Baxter, 1952; Lewis and Hoak, 1956) any beneficial effect will be lost if thawing is delayed longer than a few hours after removal from the cold environment (Edwards, 1951).

It is hoped that the opportunity will never arise for a controlled trial of different methods of treatment of local cold injury, and until such circumstances do arise opinion must, of necessity, be strongly influenced by recent experimental findings. On this basis current views on management may be summarized as follows. Immediate immobilization and rapid admission to hospital, trauma of any sort being carefully avoided; exposure of affected parts to room temperature, but, when controlled facilities are available for rapid warming to 37.5° C., these should be employed within six hours of removal of the patient from the cold environment; anticoagulant therapy, if no definite contraindication is present, together with general nursing care, adequate food and fluid intake, and prophylactic A.T.S. and antibiotics. Once the hyperaemic stage has been reached the patient will be more comfortable with the limbs exposed to a cool environment, although active cooling should be avoided, while the position of the limbs will be dictated by the amount of swelling present. Sympathectomy or ganglion-blocking drugs are not helpful in the pre-hyperaemic or hyperaemic stages, but either may be usefully employed in the post-hyperaemic state.

Accurate prognosis is difficult. In neither of the cases reported here was there any indication, when first seen, that such extensive tissue loss would occur. The fluorescein test (Lange and Boyd, 1945) was performed in Case 1 one and

five weeks after exposure, and good fluorescence was observed throughout both feet, even in toes which were already blackened. As an indication of expected tissue loss it was useless, but it certainly revealed the presence of a brisk circulation and in so doing gave strong support to Lewis's theory of direct thermal injury.

Summary

An account is given of two cases of trench-foot which occurred as a result of abnormal exposure in peacetime England.

It appears likely that trench-foot, immersion foot, and frostbite are but variants of the same clinical condition, the most important aetiological factor being in all cases a direct noxious effect of cold.

Recent experimental evidence favours early rapid warming to body temperature as the most effective form of treatment, and, provided suitable facilities are available to avoid overheating, the clinical application of this principle is advocated.

Our thanks are due to Dr. K. O. Black for permission to publish Case 1 and Dr. B. Branford Morgan for permission to publish Case 2. We are grateful to the Director of the Meteorological Office, Air Ministry, for details of weather conditions at the relevant times; and to Mr. N. K. Harrison for the photographs.

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The Institute of Dermatology held an open day on April 21 at St. John's Hospital for Diseases of the Skin, London. The object was to show visitors, both medical and lay, the research which is being done there. This includes research into the reaction of normal and abnormal skin to light which has made it possible to define light sensitivity in terms of very narrow wavelengths; work on the use of radioactive isotopes in the treatment of haemangiomata; investigations on epidermal sensitivity and the use of patch tests, particularly for cement and alkali dermatitis and cheilitis due to lipstick; and studies of the application of histochemical techniques to the detection of enzyme activity, and of cytodiagnosis to the diagnosis of skin lesions. There were also demonstrations of the L.E.-cell phenomenon, of methods of diagnosing scabies and ringworm of the nails, and of research on the penetration of ringworm fungi into hair keratin. Other studies included a survey of the serum proteins in skin diseases, particularly psoriasis, and an investigation of the changes in the nucleic acids and respiratory enzymes brought about by ultra-violet irradiation of the skin. There was also an exhibition of ointment bases. Although the main object of the open day was to demonstrate research, the opportunity was taken to display the very large collection of coloured photographs and wax moulages which is being built up for teaching purposes.

THE POTTER SYNDROME OF RENAL AGENESIS

BY

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In 1946 Potter published a series of 20 cases in infants in whom bilateral absence of the kidneys was associated with a hypoplasia of the lungs and a characteristic facies. Her description of the facies, unfortunately labelled by some as the facies renalis, cannot be bettered, and reads: "The face most characteristically exhibits an increased space between the eyes, a prominent fold which arises at the inner canthus and sweeps downwards and laterally below the eyes, an unusual flattening of the nose, excessive recession of the chin, and moderate enlargement and decreased chondrification of the ears. The face gives a suggestion of premature senility." Thus, as in mongolism, recognition of this unusual appearance and knowledge of its implications are of the utmost importance in prognosis. Such children are generally regarded as rare occurrences, but recent experience in this unit suggests this may not be so, and details of five such cases are given in the accompanying Table. Two of the mothers are known to have had normal children subsequently.

Discussion

These five infants demonstrate several features typical of this condition. Unlike most mothers of children with congenital abnormalities, all these mothers were primiparae and, at the ages of 20, 20, 21, 28, and 30, none remarkably late in child-bearing. In three, presentation was by breech, again quite frequent with this abnormality. In three a lack of amniotic fluid was apparent, and this, too, is exceedingly common, though not universal. Selby and Parmelee (1956) have described the case of an infant with this condition born tightly encased in intact membranes devoid of fluid, whilst in other reports the quantity of fluid appears normal, so that, whatever the origin of amniotic fluid, it can receive no more than a contribution from the foetal urine, as has been suggested in the past. There is a strong sex linkage, most instances being in males, and the child is most often born prematurely, weighing less even than the dates might lead one to expect. About two-thirds (Davidson and Ross, 1954) are liveborn but live for only a few hours, as the lungs are incapable of supporting life. Only a few have lived beyond a day, but Woolf and Allen (1953) have recorded an exceptional instance of a child living without kidneys for 39 days. Renal agenesis has been recorded several times in two members of the same family (Schmidt *et al.*, 1952; Baron, 1954) and in one of twins (Levin, 1952) —the twins shared the same placenta and were thought probably to be identical.

As might be expected, other congenital malformations are often found in these infants, but their pattern is again unusual, the majority involving the lower limbs and to a less extent the anus and external genitalia. Neither the typical facies nor the lung changes occur in every case, although most of those described since 1946 have done so. Of the 232 cases collected by Davidson and Ross (1954) only about 20% had no other notable evidence of abnormality and a further 10% had talipes, toe deformity, and other minor abnormality. Most of the lower-limb abnormalities are gross: absent kidneys are commonly associated with apus, monopus, and sirenomelia (the mermaid deformity). Whilst many of these are associated abnormalities, some may be secondary to the lack of amniotic fluid. Denis Browne (1955) believes abnormal mechanical intrauterine

Details of Cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Mother's age	20	21	30	28	20
Pregnancy	First	First	First	First	First
Blood group	O, Rh positive	A, Rh positive	O, Rh positive	O, Rh negative	O, Rh positive
Presentation	Breech	Vertex	Breech	Breech	Vertex
Delivery	5 days after version to vertex at 34th week	Spontaneous at 33rd week	Caesarean section at term (foetal distress)	Spontaneous at term	Spontaneous at term
Quantity of liquor	Reduced	Reduced	" Very little "	Not remarkable	Not remarkable
Infant's weight	3 lb. 10 oz. (1,640 g.)	3 lb. (1,360 g.)	4 lb. 13 oz. (2,180 g.)	3 lb. (1,360 g.)	4 lb. 4 oz. (1,927 g.)
,, sex	Male	Male	Male	Male	Male
,, condition	Stillborn (died during labour)	Blue asphyxia	Asphyxiated. Atelectasis	Stillborn (died during labour)	White asphyxia
,, duration of life	—	15 hours	4½ days	—	115 minutes
,, facies	Typical	Typical	Typical	Normal	Typical
Necropsy: Renal tract and other pelvic organs	Kidneys, ureters, renal arteries absent. Minute bladder. Seminal vesicles not identified	Kidneys, ureters absent. Atretic bladder.	Left kidney, ureter, vas and seminal vesicle absent, right ureter and aplastic kidney present (see photograph). Right vas and seminal vesicle present. Small bladder without exit	Kidneys and ureters absent	Kidneys and ureters absent. Bladder not identified, rudimentary prostate
Lungs	Premature	Small and collapsed	Expanded, slight hypoplasia	No information	Airless and hypoplastic
Other findings	—	Abnormal tricuspid valve (two cusps only, thick, fused with short thick chordae)	—	—	Bilateral talipes. Flexion deformity metacarpal joints left hand. Cysts of brain

With the exception of the mother of Case 5, who had a thrush vaginitis in early pregnancy and anaemia and a prolapsed disk later, there was nothing of note in the family histories, and their health before and during pregnancy was normal.

pressures cause such abnormalities as talipes, scoliosis, and other malpositions of the limbs, whilst an increase in hydrostatic pressure, by interfering with venous return, will produce stiffness, contractures, and perhaps even arthrogryposis, all found in these children. Malformations of the heart appear to be uncommonly associated with this condition. Davidson and Ross (1954) discovered reports of two examples of coarctation of the aorta (infantile type), two of double inferior vena cava, five of the various septal defects, one each of aortic atresia, pulmonary atresia, and transposition, and three of unspecified abnormality.

Both kidneys and ureters are usually absent, the position of the kidneys being occupied by flat disk-like adrenals. Where there is a ureter some identifiable renal tissue may develop, the stimulus of the ureteric bud from the Wolffian duct being apparently necessary (in humans) before differentiation of nephrogenic tissue into glomeruli and secretory tubules can occur (see photograph). Other Wolffian duct derivatives are usually present, as are the gonads. In the female the backward extension of the Müllerian ducts is often inhibited, resulting in absence of the uterus and upper vagina. The bladder is usually present as a narrow thin-walled sac extending up towards the umbilicus; the rectum and lower bowel or anus are not infrequently undeveloped or imperforate. The hypoplastic lungs resemble those of a younger foetus. It is generally considered that the cause of these abnormalities is the action of some blighting agent on the developing foetus at about the fourth to sixth week, and in this connexion both Osmond (1955) and Sylvester and Hughes (1954) have reported instances where the mother has confessed to taking abortifacients at this time.

Case 3. Photographs showing the facies and the disk-like adrenals, right ureter, and aplastic kidney.

In an attempt to discover the frequency of this condition the records of the last ten years were examined, and these five cases were discovered—the earliest in 1949. During these ten years there have been approximately 6,580 deliveries, with 166 neonatal deaths and 211 stillbirths (not excluding the occasional foetus of less than 28 weeks' gestation). In the same period there have been nine anencephalic children and nine with severe intestinal abnormality (obstruction, exomphalos, etc.), but it must be pointed out that this hospital, as a teaching hospital, accepts an unnatural proportion of primiparae and complicated pregnancies. Potter (1946) gives an incidence for the Chicago Lying-in Hospital of 0.3 per thousand births, whilst in this country Sylvester and Hughes (1954) found four examples in 9,440 deliveries, and Bound *et al.* (1956) 2 in 10,028 deliveries (Butler, personal communication).

Summary

Five infants with bilateral renal agenesis have been born in the maternity wards of a teaching hospital in the last ten-year period, an incidence of 0.75 per thousand deliveries and 1.6% of the stillbirths and neonatal deaths. The case histories and post-mortem findings are summarized and a brief review of the salient features of this curious abnormality is given.

I am grateful to Dr. J. Forest Smith for permission to publish these case records and to Drs. H. Spencer and J. Macmillan for details of their findings at necropsy.

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SEVERE SHOCK SYNDROME DUE TO CONTAMINATED INFUSIONS

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The use of infusions and transfusions has become a daily routine in medical practice, and there is a tendency to forget that they are not devoid of danger. There have been several reports in the literature concerning the inherent dangers of transfusions, and the number of fatalities they exact has been estimated to be at least as high as that of appendectomies (*New Engl. J. Med.*, 1951). There have been fewer reports concerning the dangers of infusions. Having observed a severe incident of this sort, we are reporting it because we feel that it can occur at any time, and, unless recognized early and treated vigorously, can be rapidly fatal.

On July 31, 1957, six patients in our ward were receiving infusions of corticotrophin and chlorpromazine in Darrow's solution. Five of them developed reactions ranging from a mild disturbance to very severe shock, while no reaction was noted in the sixth patient.

Case 1

A woman aged 45 had a herniated lumbar disk, which did not respond to the usual conservative treatment. Previous to the present incident she had received 70 units of corticotrophin in all and was in excellent general condition. At 11.30 a.m. on July 31, 1957, an intravenous infusion of 10 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution was started. At 1.30 p.m., after having received about 100 ml. of the solution, she was seized by a violent chill, and her temperature rose to over 39° C. (102.2° F.). She complained of headache and abdominal pains, her face was very flushed, and she started to vomit. The infusion was immediately stopped, and, in the belief that it was an ordinary pyrogenic reaction, an injection of 0.01 g. of morphine was given. However, her condition did not improve; the flushing was very marked, the pulse was around 140 a minute, and the blood pressure, to our surprise, was 60/30, her normal pressure being 110/80. The low pressure persisted despite 50 mg. of ephedrine, and within 45 minutes from the beginning of the reaction an infusion of noradrenaline, 10 mg. in 500 ml. of saline, had to be started. With a small quantity of noradrenaline the systolic blood pressure could be kept at 100–110, but at every attempt to stop the noradrenaline the pressure immediately fell to below 60–70 systolic. During the first two hours the appearance of the patient changed considerably, the temperature came back to normal or below, and the abdominal pains and vomiting stopped. The flush persisted, sweating was very profuse, and the picture was one of severe vascular collapse. During the next 12 hours the shock persisted.

Since the clinical picture did not suggest bacterial infection, and because of a preliminary laboratory report hinting at a possible fungal contamination, no antibiotics were given. After 12 hours an intravenous infusion of cortisone was added. The systolic blood pressure rose immediately to 190–200, and it was possible to reduce the quantity of noradrenaline, but not to withdraw it. On the following day the patient's general condition improved gradually, but the shock persisted, necessitating continuous noradrenaline for 30 hours. Thereafter noradrenaline was stopped and the blood pressure remained around 90/70 for a further 12 hours and then returned to normal. Recovery was uneventful and without sequelae.

During the shock she received in all 30 mg. of noradrenaline and 105 mg. of cortisone (75 mg. of this intramuscularly). The day after the onset of the reaction the infusion solution was found to be contaminated with a viable coliform bacterium sensitive to several antibiotics. Streptomycin, 2 g., was given the same day and 1 g. on each of the next four days.

Laboratory data during the reaction:—There was no evidence of intravascular haemolysis; blood bilirubin, 0.4 mg./100 ml.; urinary urobilinogen, normal; urine examination, normal. Blood electrolytes: NaCl, 550 mg./100 ml.; K, 15.4 mg./100 ml.; CO_2, 48 vols. %.

Case 2

A woman aged 47 with Guillain–Barré syndrome had received 100 units of corticotrophin during the seven days previous to July 31, 1957. At noon on that day an infusion of 10 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution was started. About two hours later, after receiving about 120 ml. of the solution, she had a violent reaction, with chills, fever up to 39° C. (102.2° F.), headache, abdominal pains, nausea, flushed face, and rapid pulse. The blood pressure was 60/40 (her normal pressure was 165/90). There was no response to ephedrine, and within half an hour from the onset an infusion of noradrenaline was started. During the next few hours all the previously mentioned symptoms disappeared, with the exception of very profuse sweating and profound shock. Any attempt to discontinue the noradrenaline resulted in blood pressure around 30/20. After 12 hours, intravenous and intramuscular cortisone was added with good results. The blood pressure rose to 190–200 systolic, and it was possible to slow the noradrenaline drip but not to stop it. After 24 hours 2 g. of streptomycin was given, and was continued on the following days. The patient's condition improved gradually, and the noradrenaline was discontinued 24 hours after it was started, the blood pressure remaining around 95/60 for another 10 hours and then returning to normal. The patient made an uneventful recovery. She received in all 20 mg. of noradrenaline, 30 mg. of cortisone intravenously and 25 mg. intramuscularly.

Laboratory data during the reaction:—Urine examination, normal; blood bilirubin 0.4 mg./100 ml.; blood electrolytes on the second day of the reaction: NaCl, 594 mg./100 ml.; K, 12.4 mg./100 ml.; CO_2, 49 vols. %; blood electrolytes on the third day of the reaction; NaCl, 598 mg./100 ml.; K, 10 mg./100 ml.; CO_2, 36 vols. %; no evidence of haemolysis.

Case 3

A woman aged 34 had myasthenia gravis and thymoma which reacted poorly to irradiation and neostigmine. Two days previously corticotrophin infusions were started and she had received 30 units. On July 31, 1957, an infusion of 15 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution was started. This infusion, in common with all the other infusions, was discontinued because of the reactions in the first two patients. She had received about 100 ml. of the solution. The reaction began an hour later with fever, chills, flushing, etc., and continued, as in the other patients, with profuse sweating and shock. The noradrenaline drip was started within 30 minutes of the beginning of the reaction and continued for three hours, when it was discontinued and the blood pressure kept at about 80–90 systolic for eight hours with intramuscular injections of ephedrine 50 mg. (three injections). Later the noradrenaline drip had to be reinstalled for another 37 hours. This was the most difficult case of the five, as the

shock lasted for almost 48 hours and was complicated by an exacerbation of the myasthenia gravis, necessitating hourly injections of 1 mg. of neostigmine, while previously she had been stable with 5 tablets of neostigmine (15 mg. each) a day. She received in all 40 mg. of noradrenaline, 100 mg. of cortisone, and, starting the day after the beginning of the reaction, tetracycline, 1 g. a day for four days. She made a complete recovery without sequelae.

Laboratory data:—Urine, normal; no haemolysis; blood bilirubin, 0.5 mg./100 ml. Blood electrolytes: NaCl, 520 mg./100 ml.; K, 12.2 mg./100 ml.; CO_2, 59 vols. %.

Case 4

A girl aged 19 with ulcerative colitis had received 110 units of corticotrophin previous to July 31, 1957. On that day an infusion of 10 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution was begun. After one and a half hours and after about 100 ml. of the solution had been given the reaction started with chills, fever, vomiting, and rapid thready pulse, as in the other patients. The blood pressure was 60/40. A noradrenaline drip was started, and after she had received 5 mg. of noradrenaline in eight hours it could be discontinued. The pressure stayed low for some hours, then went up to normal. No cortisone was given. She continued to receive corticotrophin for a few days and made a good recovery.

Laboratory data:—No signs of haemolysis; blood bilirubin, 0.4 mg./100 ml.; urine, normal.

Case 5

A woman aged 42 with macroglobulinaemia (Waldenström disease), thrombocytosis, and nephrotic syndrome had not received corticotrophin for the previous 10 days to July 31, 1957.

On that day she received an infusion of 25 units of corticotrophin and 50 mg. of chlorpromazine in 300 ml. of Darrow's solution. After more than two hours and after about 100 ml. of the solution had been given the infusion was stopped. Her reaction started a quarter of an hour later. This was the mildest case of all the five. She had the prodromal signs with chills, fever, abdominal pains, vomiting, headache, flushed face, and rapid pulse, but her systolic pressure never fell below 80. Neither noradrenaline nor cortisone was given. She received 50 mg. of ephedrine intramuscularly and in four to five hours the blood pressure returned to normal, and the nausea and vomiting stopped. The next day no signs of the reaction remained.

Bacteriological Findings

The five suspected bottles of Darrow's solution were marked with the same sterilization date, nine days before. The bottle of the sixth patient, who did not show any reaction, was of another date. Within five hours of the reaction they were sent for bacteriological examination. At first sight nothing unusual could be detected; but with the help of a strong light a slight turbidity could be seen. Cultures were prepared from three of the suspected solutions and from all of them a coliform bacterium was grown. The solution received by the sixth patient was sterile. Unopened transfusion sets bearing the same sterilization date as those used with the contaminated bottles were examined and found sterile. In order to exclude exogenous contamination of the solution by the corticotrophin and chlorpromazine introduced, an unopened bottle of Darrow's solution bearing the same date as the contaminated ones was cultured and the same coliform bacterium was again isolated. This undoubtedly incriminated the Darrow's solution autoclaved nine days previously as the source of contamination.

All infusion solutions used in this hospital are prepared in the central supply department and sterilized in a big autoclave heated by steam under pressure. During the eight years that this department has been functioning there have occurred occasional pyrogenic infusion reactions, but this was the first time that solutions were found non-sterile. Investigation revealed that the sterilization by autoclave nine days previously was defective owing to a temporary arrest of steam supply which passed unnoticed. The following day some bottles aroused the suspicion of the autoclave attendant. They were cultured and found contaminated, partly with fungi. All bottles of this batch were immediately discarded. Five bottles unfortunately did escape detection, with the results described above.

The coliform bacterium was a motile, non-spore-bearing, Gram-negative rod. The following biochemical reactions were noted: Indole +; M.R. +; V.P. −; Simmons's citrate +; urea −; H_2S not produced on T.S.I. agar; lactose was fermented after one day to acid and gas. Not haemolytic. No growth at 4° C. Good growth at 25° C. and 37° C. This bacterium shows all the characteristics of *Escherichia coli*, except the ability to grow on ammonium citrate. Since the question of nomenclature is yet under discussion it will be referred to as coliform bacterium. It was sensitive *in vitro* to streptomycin, chloramphenicol, and tetracycline.

Darrow's solution contains 260 mg. of KCl, 400 mg. of NaCl, and 500 mg. of sodium lactate per 100 ml. The latter may serve as an adequate source of carbon for bacteria with simple nutritional requirements, but the solution is deficient in nitrogen. Nevertheless growth was obtained when Darrow's solution was experimentally inoculated with small numbers (10–20) of the same coliform bacterium. After 48 hours at room temperature (26–28° C.) countings resulted in 6 to 8 million viable organisms per ml., remained on this level for a week, and later on declined. All experimentally infected solutions remained clear. Although reagents of *B.P.* grade were used for the preparation of the Darrow's solution, apparently enough nitrogen-containing impurities were present to make bacterial growth possible. These findings are in accordance with those of Garvie (1955), who found that *E. coli.* was able to multiply in phosphate buffer containing citrate or lactic acid, or even in phosphate buffer only.

Discussion

Reactions following the introduction of contaminated fluids into the blood stream vary considerably, according to quantity and type of the micro-organisms involved. One possible result is that of infection, as illustrated by Rabinowitz and Shiffrin (1953), who report a series of ward infections ranging from local suppurations to fatal meningitis arising from a contaminated infusion solution. Michaels and Ruebner (1953) report two cases of pyrexia associated with a prolonged intravenous infusion which was contaminated.

Another possibility is that of a short-lived "pyrogenic" reaction. Doubtless many slightly contaminated infusions pass unrecognized this way. A reaction less intense than that of Case 5 might fall in this category.

The complication to which we want to draw attention here is that of mild or severe shock of rapid onset, due to the endotoxins contained in the solution or liberated by the rapid dissolution of the bacteria in the blood stream.

All our patients presented a uniform type of reaction. It started with chills, high fever, restlessness, flushing, abdominal pains, and vomiting, with a rapid pulse. This violent reaction lasted for about two hours, but concomitant with it and masked by it there was a rapid development of severe shock. Less than half an hour after the onset of the symptoms the systolic blood pressure measured between 30 and 60 mm. Hg. After two to three hours the violent reaction abated, the temperature returning to normal or below, but there persisted severe shock with profuse sweating. We would emphasize that the shock is not clinically apparent in the first two or three hours, and, unless looked for, precious time may be wasted and life-saving treatment delayed.

This syndrome is essentially the same as that described by Whitby (1949), Borden and Hall (1951), Stevens *et al.*

(1953), Braude *et al.* (1953), McEntegart (1956), and others after the transfusion of contaminated blood. The blood in those cases was contaminated by cold-growing micro-organisms, most of them Gram-negative. The effects of endotoxins of Gram-negative bacteria have been extensively studied in animals. The main manifestations were fever, diarrhoea and vomiting, hypoglycaemia, changes in leucocyte distribution, and shock, resulting in death. Ebert *et al.* (1955) injected meningococcus toxins intravenously into dogs, producing a precipitous fall in blood pressure. They concluded that this was due to venous pooling of the blood in the viscera. The shock was treated successfully with noradrenaline. Augmentation of the blood volume was less effective, and cortisone was of no help. Weil *et al.* (1956) produced shock in dogs with coli endotoxin. They also explained this phenomenon by venous pooling and were able to correct it by metaraminol.

The role of adrenal damage or insufficiency in the production of shock in those cases of acute septicaemia seems to be of less importance than previously thought. Of the various necropsy reports of fatal contaminated transfusion reactions only one case showed unilateral adrenal damage (McEntegart, 1956). None of the dogs in the experiments of Ebert *et al.* (1955) showed gross adrenal lesions. Although no extensive studies in this direction were done in our patients, results of serum sodium and potassium estimations did not point to adrenal insufficiency.

The severity of the shock seems to be in direct proportion to the quantity of endotoxins introduced into the blood stream. The effect is the same whether the bacteria are dead or alive. The endotoxins of most of the Gram-negative bacilli have the same action—for example, the meningococcus and *E. coli*.

The fatality rate in reported transfusion accidents due to contaminated blood is quite high, especially when Gram-negative bacilli are concerned. Stevens *et al.* (1953) report 32 cases assembled from the literature, including their own, of which 65% ended fatally. Two fatal cases are described by McEntegart (1956).

All our patients recovered. As the reactions began in the early hours of the afternoon, at a time when all the doctors were in the ward, and occurred almost simultaneously, immediate attention was directed to them and treatment was started early. Within 30 to 45 minutes of the beginning of the reaction all the patients in shock were being given noradrenaline drips.

In our opinion this early treatment is one of the main factors that contributed to the recovery, the importance of the time factor in shock being well known. Another factor, not given to comparison or measurement, is the quantity of endotoxins introduced.

The amount of noradrenaline given was not great, an average of 20 mg. per 24 hours being sufficient. Cortisone was found to be of definite value, probably owing to its potentiating effect on noradrenaline, as experimentally demonstrated by Kurland and Freedberg (1951), although, as mentioned above, it has no direct effect on the shock.

Antibiotics were started only the day after the beginning of the reaction and did not seem to play an important part in the treatment.

Because of the severity and potential dangers of this condition no effort should be spared in its prevention. Since no macroscopic abnormalities can be seen in the contaminated solutions, the strictest control of sterilization procedures is essential, with sterility checks of every batch of fluids before distribution.

Summary

Five cases of mild to severe shock due to the intravenous infusion of Darrow's solution contaminated with coliform bacteria are reported. Attention is called to the rapid though masked onset of circulatory collapse, and its mechanism discussed. All patients were successfully treated with noradrenaline and cortisone. The importance of early recognition and treatment of the shock is emphasized.

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Medical Memorandum

Incontinentia Pigmenti (Bloch-Sulzberger)

Incontinentia pigmenti is a rare developmental anomaly involving the skin and other ectodermal tissues. The first case under this name was described by Bloch (1926) and again by Sulzberger (1928), though in 1925 Bardach had reported two cases of an identical condition under the diagnosis of systematized naevus formation. In view of the apparent rarity of the condition the following three cases are described.

CASE 1

A female infant, the fifth child of healthy parents, was born after a short labour. During pregnancy the mother had suffered from hyperemesis and mild toxaemia. The birth weight was 7¼ lb. (3.4 kg.). Soon after birth a slight discharge was noticed from both eyes; otherwise the child appeared normal. On the second day she developed a generalized rash, and the following day there was twitching of the right arm and right side of the face; as a result of this she was admitted to hospital.

On examination a rash was seen over her trunk and limbs: this consisted of raised erythematous areas, some surmounted with papules and some with pustules. Certain of these erythematous areas showed desquamation and yellow-brown pigmentation (Fig. 1). In addition there was twitching of the right arm and right side of the face; the cry was cerebral in type. No other abnormality was found.

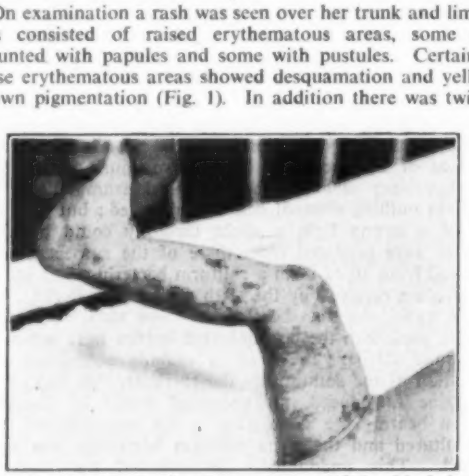

FIG. 1.—Case 1, showing the appearance of the skin lesions.

A diagnosis was made of cerebral birth trauma with an associated infective erythema, and treatment was begun with phenobarbitone and chlortetracycline. The twitching soon ceased but the rash persisted. Because of this failure

to respond to treatment and the rather unusual appearance of the lesions the baby was seen by the dermatologist, and incontinentia pigmenti was diagnosed.

When she was seen in the out-patient department at the age of 2 months the erythematous areas had almost disappeared, but linear verrucous growth had developed on the legs and feet: there was no evidence of pigmentation. Attempts to persuade the mother to bring the baby back for further examination have not been successful, but she has reported that the child is well and that the skin is clear.

CASES 2 AND 3

These patients were female twins born four years ago; their birth weights were 5 lb. 12½ oz. and 5 lb. 3½ oz. (2.62 and 2.37 kg.) respectively. The delivery was uneventful and no abnormalities were noticed at birth in either infant. At the age of 1 month they both developed sore buttocks, and two weeks later blisters of various sizes appeared on their legs, most of which subsequently burst.

On admission they had an identical skin condition consisting of pemphigus-like blisters; many of these had broken and the raw areas were covered by a dry slough. These lesions occurred over most of the body from the waist downwards. The areas of the skin not affected were erythematous and thickened, and warty growths were found adjacent to the anus. No other abnormality was found in either baby. The appearance of the rash suggested the possibility of syphilis, but the Wassermann tests of the mother and twins were all negative, and no spirochaetes were seen in swabs taken from the lesions. A diagnosis of incontinentia pigmenti was suggested, and a skin biopsy from the left leg of Case 2 was reported on as follows: "There is a flattening of the dermo-epidermal border, and only in a few places short epidermal pegs are seen. There are no pigment granules in the basal layers of the epidermis. In the cutis vera there are numerous fusiform and spider-shaped cells with finely granular acidophil cytoplasm. Only exceptionally brown pigment granules are seen in such cells. A silver impregnation showed somewhat more argentophil granules in these cells. The findings are compatible with the diagnosis of incontinentia pigmenti" (Fig. 2).

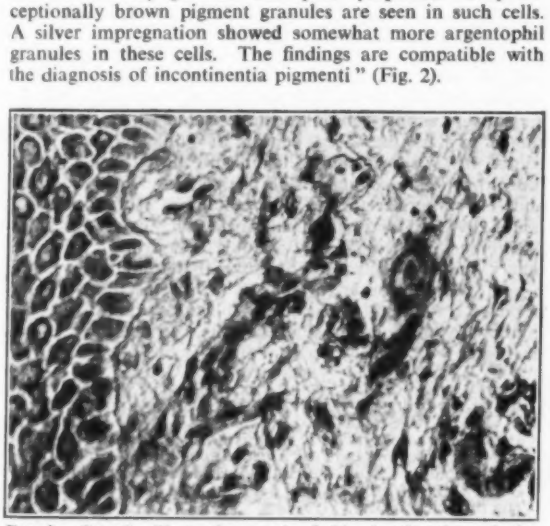

FIG. 2.—Case 2. Photomicrograph of skin showing the melanin-containing chromatophores in the corium.

After discharge from hospital the skin condition recurred several times during the first year, but both babies have been completely clear for the past two years. At their last examination neither child had any residual rash or pigmentation, or any evidence of alopecia or dental hypoplasia.

DISCUSSION

The first case of incontinentia pigmenti in this country was described by Haber (1948, 1949). Carney (1951) was able to find 32 cases in the literature; to these he added a further five. Franklin (1952) also reviewed the literature and added a case of his own, and Kitamura *et al.* (1954) described 21 hitherto unreported cases from Japan. Other papers on the subject are those of Loveman *et al.* (1952), Epstein *et al.* (1952), and Bambridge (1953).

Incontinentia pigmenti occurs predominantly in female infants. All the 21 cases of Kitamura *et al.* (1954) were females, as were 33 of the 37 cases reviewed by Carney (1951).

The condition is often present at birth, but may appear at any time during the first two years. The initial lesion is usually an erythematous rash with superimposed bullae and papules, tending to develop in lines and patches, and may be mistaken for a septic skin condition. This stage tends to persist for weeks or months, with periodic improvement and relapse. Finally, areas of pigmentation appear, either direct from the initial bullous lesions or through an intermediate stage in which linear warty growths develop.

The fully developed condition consists of irregularly scattered areas of slaty-grey or chocolate-brown pigmentation arranged in a series of lines, whorls, and spider formations. These lines do not correspond to nerves or blood vessels, and may cross the midline. In a few cases this is present at birth. The pigmentation tends to fade gradually, but the length of time varies. The course of Cases 2 and 3 would suggest that in some instances definite skin pigmentation does not always appear. In Case 1 it is presumed that this may develop later, as the child is still only 5 months old.

Other ectodermal and mesodermal developmental abnormalities may be associated with the skin pigmentation: alopecia, mental retardation, congenital heart disease, various paralyses, and frequently deficient dentition have all been reported. Occasionally there is a familial history, the disease having been recorded in twins and also in a father and his two daughters (Naegeli, 1927).

The aetiology remains obscure. Bloch (1926) considered that incontinence of the basal cells of the epidermis allowed the melanin to diffuse into the corium, where it was gathered up by the chromatophores. Haber (1952) suggested the possibility that the condition was due to a viral infection of the mother during pregnancy.

The histology of the three stages has been adequately described by Carney (1951). In the early erythematous stage microscopy shows a non-specific acute inflammatory reaction with vesiculation. The epidermal vesicles are often filled with polymorphonuclear eosinophils. The basal-cell layer contains only small amounts of melanin. Examination of one of the verrucous lesions shows hyperkeratosis and acanthosis typically.

The histology of the final pigmented stage shows a diminution or absence of pigment in the basal layers of the epidermis but a relatively large amount of melanin in the chromatophores of the corium. Usually there is associated thinning of the overlying epidermis.

Incontinentia pigmenti is a benign condition and treatment is not required. Findlay (1952) reported the disappearance of the skin lesions with cortisone, although they had returned within three months of stopping treatment.

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Reviews

GENE STRATEGY

The Strategy of the Genes. A Discussion of Some Aspects of Theoretical Biology. By C. H. Waddington, Sc.D., F.R.S. Appendix by H. Kacser, Ph.D. (Pp. 262+ix; illustrated. 28s.) London: George Allen and Unwin Ltd. 1957.

Within the lifetime of a middle-aged man the word "genetics" has been invented, and the subject has passed from the simple steps of early Mendelism into the limelight of modern biology. Professor Waddington (who himself has contributed much to this transformation of genetics) has produced a book which is the quintessence of modern biology; for it deals with classical problems about living things (How do organisms adapt themselves to the environment? How does the environment influence the evolution of organisms?) in the new way. These are problems which naturalists have studied for centuries. The old way to study them was to consider primarily the end-products of development. The new way is to consider primarily the process of development itself and the biochemical processes which initiate development. Genes are the templates on which organic development begins. Their strategy is to produce a single coherent organism, and not a jumble of unintegrated processes. It is one of the great miracles of biology that the assortment of hereditary units which a man inherits from his parents do co-operate to produce a man and not a monster. Professor Waddington's book describes how this miracle may happen. It is not easy reading for the amateur; some of it is not easy even for the professional. But it is well worth the effort to read, and Dr. Kacser's appendix on the physical chemistry of gene action is a significant and important contribution to our understanding of the quantitative aspects of gene strategy.

E. ASHBY.

THE PHILOSOPHY OF OSLER

The Student Life: The Philosophy of Sir William Osler. Edited by Richard E. Verney, M.B., F.R.C.P.Ed., D.R. With Forewords by John Bruce, C.B.E., T.D., M.B., Ch.B., F.R.C.S.Ed., and Alec H. Macklin, O.B.E., *M.C.*, T.D., M.D. (Pp. 214+xiii. 15s.) Edinburgh and London: E. and S. Livingstone Ltd. 1957.

The medical student, as he sets out on his long, slow, uphill journey, has to pack a good many things in his knapsack. Richard Verney recommends him to include this anthology of Osler's writings. As physician in charge of the health both of the medical students of Edinburgh University and of the nurses of the Royal Infirmary, Dr. Verney is an enthusiast with a broad view of health. He is himself susceptible to the influence of good writing, for he tells how the reading of Dr. John Brown's *Rab and his Friends* decided him to make medicine his career, drawing him to Edinburgh from the hinterland of Africa. He has found Osler's philosophy a mainstay.

Now Osler, much as he loved learning and teaching, would never have called himself a philosopher, yet he has for long occupied a philosopher's place in medical thinking. Over 50 years ago Dr. Camac published *Counsels and Ideals from the Writings of William Osler*, and Osler gave a blessing to the book which would certainly have been extended to Dr. Verney's, for Osler wrote: "In the teacher I have always valued the message of the life above the message of the pen, but if you think that a mosaic of scraps from my addresses, etc., would be of any service to young men, please do what you wish about it." The essence of the service is advice on how to become and remain a good doctor and a worthy and respected colleague and citizen. Because of his vocational addresses Osler is, in modern language, a stereotype—the successful Victorian physician and gentleman. He was the son of a parson, though not himself noted for his churchmanship. He was the product of a classical education, but not himself a classical scholar. He had a scientific training and remained an unmitigated humanist. Living through the latter half of the nineteenth century, he learned from ordered disciplined minds, while he himself could claim freedom from allegiance to any system. During a lifetime of privileged comfort he remained an individual, helping as doctor, teacher, and friend all the other individuals within the ambit of his personality. He had no need to puzzle about the foundation of the prosperous society to which he and his friends belonged, nor about the relations between State and person, nor yet about the ultimate fruits of scientific inquiry, which in his day were seen as inevitably good.

And so with nostalgia, and a little envy, the medical student or the doctor should pause as he climbs the laborious ladder to refresh himself with this new distillation of the spirit of Osler. Gratitude will easily outweigh Dr. Verney's two lapses: that of modernizing some of Osler's sentences, and that of not resisting the tempter who bade him include as a footnote 8½ pages long his own sketch of Francis Adams.

A. WHITE FRANKLIN.

GOOD GUIDES TO DRUGS

A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. By Torald Sollmann, M.D. Eighth edition. (Pp. 1,535+xi. £7.) Philadelphia and London: W. B. Saunders Company. 1957.

This is the eighth edition of a textbook which was first published in 1917. It ranks with Goodman and Gilman's book on *The Pharmacological Basis of Therapeutics*, and these two books are the best pharmacological works of reference in the world. Sollmann is now no longer young, but the book is proof that he is at least as active as ever he was, for there is no sign of deterioration in the standard he set in earlier editions. The two books are different and do not duplicate each other. While "Goodman and Gilman" is most valuable to the practising physician who is chiefly concerned in treatment, "Sollmann" is an all-round work of reference to older drugs as well as to newer ones, and contains the answers to large numbers of questions with which the doctor is so often faced.

We hear much to-day about the difficulty of the doctor in discriminating between the useful and useless medicines presented to him in a continuous stream. Actually there is a relatively simple solution to this problem. Every doctor should possess the latest edition of Sollmann, the latest edition of Goodman and Gilman, and the latest edition of the *Extra Pharmacopoeia*. If he has these four volumes and is a subscriber to the "Card Index of New Products" issued by the Pharmaceutical Society he is always in a position to find out quickly about a new drug or preparation. Very few doctors are aware of these publications, and often it does not occur to them to buy them. But they are, in fact, the solution to the doctor's dilemma, and it is surprising how easy it is for anyone using them to find the answers he seeks.

J. H. BURN.

SICKNESS IN THE FIRST YEAR OF LIFE

Morbidity and Mortality in the First Year of Life. A Field Inquiry in Fifteen Areas of England and Wales. Edited by Fred Grundy, M.D., M.R.C.P., D.P.H., and E. Lewis-Faning, D.Sc., Ph.D.(Med.), F.S.S. (Pp. 145. 18s.) London: The Eugenics Society. 1957.

This book is an account of a detailed investigation, under the direction of the medical officer of health in 13 towns and two rural areas in England and Wales, into the sickness suffered by 21,000 babies born in 1952 and into the 2,194 infant deaths occurring in 1951–3. The aims of the survey were to ascertain the amount and type of infant sickness and relate this to the social-economic background of the infant and compare morbidity and mortality rates in relation to local conditions, to ascertain the incidence of congenital malformations, and to examine whether any difference in the pattern of morbidity and mortality afforded evidence of a genetic component.

The average number of spells of sickness during the first year of life was 96 per 100 infants, and about half of these

were due to respiratory diseases. The marked gradient of morbidity with social class was almost wholly due to respiratory diseases and the infectious diseases. The rate of falling sick for infants with bad housing and bad maternal care was half as high again as for infants with good maternal care and living in "not bad" housing. The elimination of the social-economic factors still left a considerable part of the gradient with social class unexplained. The authors thought that a personal factor independent of environment might exercise a large influence on the sickness experience and that genetic or constitutional factors could be the explanation, but the inquiry failed to reveal any such genetic factors. Maternal care was an important factor in infant mortality, but birth weight was also very important. The exclusion of the premature and "inferior maternal care" groups reduced the infant death rate to 11.6 per 1,000 births. Only about 5% of the infant deaths could possibly have been avoided by better or more prompt medical attention.

Among the conclusions drawn from the data are: that special measures are needed to improve the standard of child care in the badly housed section of the community and where the maternal care is known to be poor; that it is important for parents to recognize that acute respiratory sickness in babies calls for prompt medical attention; and that better supervision is needed for the unmarried mother and her child. For further research the authors suggest that large-scale investigations of an intimate social-clinical character are necessary; they have shown such collaboration to be feasible and possible. The book is an important and interesting contribution to the study of infant health.

W. J. MARTIN.

HEART OPERATIONS

An Atlas of Cardiac Surgery. Prepared by Jorge A. Rodriguez, M.D. (Pp. 250+xii; illustrated. £6 6s.) Philadelphia and London: W. B. Saunders Company. 1957.

The author of this atlas is an experienced artist as well as a surgeon, and he has brought together a number of line and shadow illustrations of different types of cardiac operations. The work starts with surgical anatomy, the drawings being made from the author's own dissections, and then proceeds to descriptions of the instruments and special apparatus required for major cardiac surgery. This includes accounts of some of the heart–lung machines. Then follows the main part of the book, which consists of 29 different operations that were performed by almost as many surgeons in the presence of the author. As a record of up-to-date technique in cardiac work the book is excellent. There are short and clear descriptions to accompany the drawings, and though some of these are perhaps a little repetitive the reader is able to follow the procedures quite easily. It is not a book that is likely to have a wide appeal to those who do not perform heart operations, but it is of considerable value to the specialist. It is also an admirable example of how much can be described by clear and simple drawing.

T. HOLMES SELLORS.

RADIOTHERAPY IN THE U.S.A.

Manual of Radiation Therapy. By K. Wilhelm Stenstrom, Ph.D. Collected by John B. Coleman, M.D. Revised with additions and discussions by Paul C. Olfelt, M.D., and Frances Conklin, M.D. (Pp. 94+xxx. 34s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

This work is little more than a *catalogue raisonné* of the various conditions in which radiotherapy is used, with a summary of the technique under each heading. Originally collected for the benefit of the fellows in radiology of the University of Minnesota, one may well imagine that as a complement to their lectures and clinical instruction the book could be of considerable assistance. For the post-graduate student working for an English diploma in radiology, however, its value would be much less. The physical and biological groundwork, summarized in a bare 10 pages of text, would be altogether too slight for his purposes, and the technical data given in the main part of the work are insufficient to be reproducible, although they do give a clear indication of the lines on which the various lesions are treated by the authors. Apart from two diagrams and one graph, the book is entirely unillustrated, and the absence of isodose schemes to illustrate the various field arrangements advocated deprives the book of much of its value. In spite of these defects this work will undoubtedly interest British radiotherapists as indicating the methods employed by their colleagues in the United States.

W. M. LEVITT.

DOCTOR QUINCE

At Doctor Mac's: A Documentary Entertainment. By Peter Quince. (Pp. 277. 15s.) London: J. M. Dent and Sons, Ltd. 1958.

Literature owes a fair debt to tuberculosis. The disease that killed Lawrence at 44, Orwell at 46, and Keats at 25 also got rid of Little Nell and froze Mimi's tiny hand. For the novelist it has the attraction of an inevitably fatal end, sufficiently lingering to give time for manipulation of the plot, and a dramatic symptomatology to prop up the story whenever it looks like flagging. Nowadays Mimi would be packed off for a course of streptomycin and a phrenic crush, but tuberculosis is far from eradicated among the arts. Yet since Maugham wrote *Sanatorium* authors have been interested more in the personal relationships than the personal tragedies engendered by T.B., a fashion continuing with widespread public approval as recently as *Ring for Catty*. Now Dr. Quince presents, without much impediment of plot or characterization, "a documentary entertainment" depicting life in a fictitious sanatorium. This good-humoured book largely concerns a convalescent tuberculous young doctor and a pert female sufferer who seems to be something of a phthisical icicle. Among his tweedy M.O.s Dr. Quince seems undecided whether to be clinically hearty or slightly sentimental—there are descriptions of people having a jolly good vomit as well as of tiny white coffins—but the sanatorium atmosphere comes out as strongly as the smell of disinfectant that no doubt rose from the corridoors. On the whole it seems rather a chummy place, like Butlin's.

RICHARD GORDON.

Dr. Muhammad Siddique Qureshi, an expert in the art of medical abstracting, has collected in *Current Medicine 1957* (Q Publications, Karachi; pp. 212+viii, 25s.) some of the latest views on a series of medical topics for the guidance of general practitioners in Pakistan. In the selection of topics he has in mind the needs of the single-handed doctor, far from a hospital and with few technical resources. There are excellent chapters on the prevention of coronary disease; the relief of pain; abdominal pain in pregnancy; premenstrual stress; psychosomatic conditions; and many other medical problems. The book owes much to American influence and would not always have whole-hearted support in this country. But it is a useful book, written with assurance and much practical wisdom, although some of the opinions are rather extreme. That hypnosis is of singular importance has been claimed by enthusiasts from Braid onwards. Dr. Qureshi is impressed by the power of hypnosis, and goes so far as to recommend that every doctor in Pakistan should receive adequate training in hypnosis. Even if such training were desirable, which is very doubtful, it is not available in Pakistan or anywhere else. But this advocacy of hypnosis is a side-issue and need not detract from the value of this book, which deserves the close attention of general practitioners in Pakistan.

The seventy-third volume of the *Transactions of the Medical Society of London* for 1956–7 has recently been published under the editorship of Mr. Cuthbert E. Dukes. Among its contents are the Presidential Address by Dr. T. C. Hunt—an interesting survey on the subject of food and the allergic reactions it may produce; the Lettsomian Lectures for 1957 on leukaemia, given by Dr. R. Bodley Scott; discussions on such varied subjects as mammaplasty, the dangers of antibiotics, and the complications of radiological examination; and the Annual Oration, given by Sir Harry Platt, on primary malignant tumours of bone.

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THE VESICO-VAGINAL FISTULA

In Great Britain the vesico-vaginal fistula is a rare injury but it is still a cause of suffering and distress. In days gone by it was usually the result of a prolonged or difficult labour; now it is oftener caused by surgical injury or by local necrosis or sepsis following a pelvic operation. Although it is, anatomically, a very simple lesion, it may present much difficulty in repair. In some cases a cure can be effected by almost any of the techniques that have from time to time been enthusiastically sponsored, but there are others in which the fistula seemingly resists all efforts at closure; and too often the surgeon resorts to transplantation of the ureters into the colon. This procedure may sometimes give relief, but, as A. Jacobs[1] has shown from collected hospital records, it carries a 12% mortality.

The reasons for the difficulty in closing vesico-vaginal fistulae are not far to seek. The fistula may be situated at a high level, or retracted into an awkward position behind the pubic symphysis or its ramus, where it may defy the efforts of urologist and gynaecologist alike. Sometimes it is embedded in dense scar tissue, so that its repair, even if apparently satisfactory at the time, is in fact precarious and impermanent. In all cases there is a risk of sepsis from urinary infection, and in some the added difficulty of maintaining efficient bladder drainage during the critical time of healing.

Much unnecessary, although understandable, discussion has taken place on the rival merits of the vaginal, the transvesical, and the abdominal approach for repair of fistula. Each route can, in suitable cases, give good results, and so all must be considered in treatment. It is natural that the gynaecologist, the urologist, and the abdominal surgeon should each have preference for the method he regards as his own; nevertheless, the claims of the vaginal operation have special force. Not only are the results (provided the surgeon has experience of this class of work) at least as good as are those obtained by other methods, but the damage inflicted during the operation is minimal; and, even should a complete closure not be effected, a further repair by the same route is less prejudiced than would have been the case had the transvesical or the transabdominal operation been employed.

Several important publications on this subject have appeared in recent years. In a well-illustrated booklet[2] V. J. O'Conor describes 31 cases (with 29 successes) in which an abdominal approach is used. His method is to bisect the bladder in the midline and to extend the incision backwards until the fistula is reached; the surrounding tissues are then excised with "a racket-shaped incision" and the bladder suitably closed with allowance for suprapubic drainage. This method, though simple in principle, is, as O'Conor admits, not always easy in practice. It may be difficult to get access to the lower aspect of the bladder, and often there is risk of damage to the ureters because of their involvement in the scarred area.

In a recent publication[3] H. C. Falk devotes a long section to repair of fistulae. He makes a strong plea for vaginal methods; and for post-hysterectomy cases (high vaginal fistulae) he favours the Latsko operation. This consists in a denudation of an area of vaginal wall around the fistula; infolding of the bladder wall with an inner row of stitches, and approximating the anterior to the posterior wall with a second row. The result is a closure of the extreme vaginal vault. The vagina is not, however, significantly shortened, and the term colpocleisis—often used for this operation—is hardly justified. N. Mahfouz,[4] of Cairo, long recognized as a leader in this class of surgery, has recently reviewed the subject and states that in his last 300 cases "the results were invariably successful and almost always obtained at the first shot." Of the method of operation he remarks, "I have been able to tackle almost all my cases—758 besides 210 of which I kept no records—by the vaginal route. The few cases in which I failed to close the fistula from below I also failed to do so when I attempted to close it from above. The cause of failure in both routes was the immobility of the bladder produced by dense infiltrations."

In Great Britain Chassar Moir's series[5] of more than 175 cases is the largest to be reported. The aetiology is interesting. Approximately 30% were obstetrical in origin, and 70% gynaecological. Of the latter, some 40% were caused by hysterectomy, including

[1] Jacobs, A., *Proc. roy. Soc. Med.*, 1952, **45**, 33.
[2] O'Conor, V. J., *Suprapubic Closure of Vesicovaginal Fistula*, 1957, Oxford.
[3] Falk, H. C., *Urologic Injuries in Gynecology*, 1957, Philadelphia.
[4] Mahfouz, N., *J. Obstet. Gynaec. Brit. Emp.*, 1957, **64**, 23.
[5] Moir, J. C., *Amer. J. Obstet. Gynec.*, 1956, **71**, 476.
[6] —— *J. Obstet. Gynaec. Brit. Emp.*, 1957, **64**, 342.
[7] Russell, C. S., *ibid.*, 1956, **63**, 481.

the Wertheim operation. Rather surprisingly, some 25% were the result of a simple colporrhaphy, including the "Manchester" operation. 7% were caused by radium treatment, and 5% by one or other form of "sling" operation employed to correct stress incontinence of urine. The remainder originated in a wide variety of traumatic or ulcerative conditions. With two exceptions (one a high vesico-colic fistula and one a resistant vesico-vaginal fistula situated at a high level in an extremely cicatrized vagina) the vaginal approach was used. Most of his patients had been referred after multiple previous attempts at repair (8, 10, or more in some cases, and many by the suprapubic route). Some cases were remarkable for the long duration of the urinary leakage (10 or more years, and in one as much as 32 years). In a more recent publication[6] he describes inversion of the entire bladder as a complication of a large vesico-vaginal fistula, and cites two cases in which the prolapsed mass had been wrongly regarded as a uterine procidentia. All these cases were cured by vaginal operation. Scott Russell,[7] using methods similar to Moir's in a series of 50 cases, also reports a very high percentage of success in closure.

All these are remarkable results which should do much to dispel the idea that the vesico-vaginal fistula is by nature "intractable." There is, however, another side to the picture. Because the vesico-vaginal fistula is a rare injury, few surgeons now have the opportunity of developing the special skill and experience needed in this class of work. Mahfouz, whose outstanding success has already been noted, admits "in my early cases the failures were more common than the successes." Moir has this comment to make: "The vesico-vaginal fistula is, in the great majority of cases, an eminently curable lesion. But it must be treated with respect. If it is easy of access and is surrounded by soft, vascular tissue, its repair can be confidently undertaken by any operator well experienced in vaginal plastic surgery. If, however, the fistula is not of this simple type, there should be no hesitation in placing the patient in the hands of a surgeon who has had experience in this very specialized work."

There is reason to suppose that even now there are unfortunate women in the remoter parts of this country who, day in and day out, tolerate a seepage of urine believing that their condition is incurable. With the advent of the Health Service there is no longer difficulty in transferring patients from one hospital to another where facilities for special treatment are available. The vesico-vaginal fistula that has resisted an attempt at simple repair is an example of the type of case that merits this special consideration.

MAGNESIUM

The most abundant cations in the body fluids are sodium, mostly outside the cells, and potassium and magnesium, almost entirely within the cells. Deficiencies of these ions are unlikely to arise except from abnormal losses, of which the most important are gastro-intestinal. Sodium deficiency is the first to appear because the concentration of sodium in the gastro-intestinal secretions (110–150 mEq per litre) is much greater than that of the two other ions (potassium about 10 mEq per litre and magnesium only 3 mEq per litre).[1–3] In fact potassium deficiency was hardly recognized clinically until the treatment of sodium deficiency enabled patients with severe gastro-intestinal losses to survive long enough to become depleted of potassium. Now that potassium deficiencies are also treated we may expect deficiencies of magnesium to be revealed.

The problem of deficiencies of these ions must be considered in relation to what the body normally contains. This has rarely been estimated directly. A man weighing 70 kg., 20% of it fat, contains about 4,500 mEq of sodium, 3,700 mEq of potassium, and 2,000 mEq of magnesium.[4 5] These estimates are higher than earlier ones, because the amounts in bone were underestimated. Bone contains one-third of the sodium, one-tenth of the potassium, and one-half of the magnesium in the body.

The clinical problems of sodium depletion and potassium depletion are now well recognized and they have been studied experimentally. The problem of magnesium deficiency, on the other hand, is still in its infancy. J. Leroy[6] was the first to show that in growing animals a lack of magnesium is lethal. E. V. McCollum and his associates[7 8] showed that magnesium deficiency in young rats and dogs led to

[1] De Beer, E. J., Johnston, C. G., and Wilson, D. W., *J. biol. Chem.*, 1935, **108**, 113.
[2] Levey, S., Abbott, W. E., Krieger, H., and Davis, J. H., *J. Lab. clin. Med.*, 1956, **47**, 437.
[3] Nadler, C. S., *Amer. J. med. Sci.*, 1953, **226**, 88.
[4] Widdowson, E. M., McCance, R. A., and Spray, C. M., *Clin. Sci.*, 1951, **10**, 113.
[5] Forbes, G. B., and Lewis, A. M., *J. clin. Invest.*, 1956, **35**, 596.
[6] Leroy, J., *C.R. Soc. Biol. (Paris)*, 1926, **94**, 431.
[7] Kruse, H. D., Orent, E. R., and McCollum, E. V., *J. biol. Chem.*, 1932, **96**, 519.
[8] Orent, E. R., Kruse, H. D., and McCollum, E. V., *Amer. J. Physiol.*, 1932, **101**, 454.
[9] Cunningham, I. J., *N.Z. J. Sci. Technol.*, 1936, **18**, 419.
[10] Blaxter, K. L., Rook, J. A. F., and MacDonald, A. M., *J. comp. Path.*, 1954, **64**, 157.
[11] Duckworth, J., and Warnock, G. M., *Nutr. Abstr. Rev.*, 1942, **12**, 167.
[12] McArdle, B., *Brit. med. Bull.*, 1956, **12**, 226.
[13] Vitale, J. J., White, P. L., Nakamura, M., Hegsted, D. M., Zamcheck, N., and Hellerstein, E. E., *J. exp. Med.*, 1957, **106**, 757.
[14] —— —— —— —— —— —— ibid., 1957, **106**, 767.
[15] Flink, E. B., McCollister, R., Prasad, A. S., Melby, J. C., and Doe, R. P., *Ann. Int. Med.*, 1957, **47**, 956.
[16] —— Stutzman, F. L., Anderson, A. R., Konig, T., and Fraser, R., *J. Lab. clin. Med.*, 1954, **43**, 169.
[17] Nabarro, J. D. N., Spencer, A. G., and Stowers, J. M., *Quart. J. Med.*, 1952, **21**, 225.
[18] FitzGerald, M. G., and Fourman, P., *Clin. Sci.*, 1956, **15**, 635.
[19] Card, W., in Ciba Foundation Colloquium on "Water and Electrolyte Metabolism in Relation to Age and Sex," 1958, in press.
[20] Hammarsten, J. F., and Smith, W. O., *New Engl. J. Med.*, 1957, **256**, 897.
[21] Hamburger, J., and Richet, G., *Rev. franç. Et. clin. biol.*, 1956, **1**, 39.
[22] Wacker, W. E. C., and Vallee, B. L., *New Engl. J. Med.*, 1957, **257**, 1254.

increased nervous excitability and convulsions which were usually fatal. In growing animals fed on diets very low in magnesium, the concentration of magnesium did not change in the soft tissues, though it fell in the serum and in bone,[9 10] suggesting that the skeleton provided a reserve of magnesium.[11]

There have been a number of reports claiming to describe magnesium deficiency in patients, but in most of them the diagnosis was based on a low concentration of magnesium in the plasma and there were no balance studies to support the claims. As with potassium, the plasma levels of magnesium are by no means a certain guide to the amounts of the ion in the cells, nor can a satisfactory response to the administration of magnesium necessarily be taken as evidence of depletion: in familial periodic paralysis the plasma potassium is generally reduced and the attacks respond to potassium, but there is no deficit of potassium in the body.[12] The factors determining the level of magnesium in the plasma have hardly been investigated. Some recent observations point to an interrelationship between magnesium requirements, cholesterol intake, and thyroid hormone.[13 14] A low concentration of magnesium in the plasma may be associated with certain nervous symptoms, which E. B. Flink and colleagues[15] list as follows: muscular twitching and tremor with involuntary movements; agitation and even delirium with hallucinations; and finally convulsions and coma. Many of the patients have been alcoholics with delirium tremens, in whom there was no obvious reason for depletion of magnesium; only a few have had abnormal gastro-intestinal losses.[16] The symptoms have responded, gradually or suddenly, to the administration of magnesium.

Deficits of magnesium, when measured, have been 50–70 mEq, or less, in patients with gastro-intestinal losses and with diabetic acidosis.[17] In an experimental study of magnesium deficiency in man, M. G. FitzGerald and P. Fourman[18] found that losses of this magnitude were of little significance. Larger losses would be difficult to produce experimentally, because when the subjects were deprived of magnesium the faecal and urinary losses became very small, less than 3 mEq daily. Larger deficits of the order of 200 mEq almost certainly can arise if the losses extend over several weeks,[19 20] and such deficits may cause tremor and confusion.

The problem of magnesium intoxication has attracted even less attention than that of deficiency, though it probably complicates both chronic and acute renal failure. The effects on the T wave of the electrocardiogram of a raised magnesium level in the plasma are similar to the effects of a raised potassium level, and this must sometimes explain the disproportion between the elevation of the T waves and the hyperkalaemia in renal failure. In addition, excess of magnesium increases the atrio-ventricular conduction time. Magnesium intoxication produces clouding of consciousness and stupor, and it may possibly contribute to the mental disturbances of renal failure.[21 22] Unfortunately progress has partly been held up for lack of any method for determining magnesium that is both rapid and accurate. A new method, using a flame spectrometer,[22] promises to provide much of the missing information.

LIFE EXPECTATION OF RADIOLOGISTS

The National Research Council of the U.S.A. in its summary report on the biological effects of atomic radiation[1] states that shortening of the life span may result from exposure to radiation. This is not only as a result of specific tissue damage, but also as a result of such general factors as lowered immunity or premature ageing. The similar report of the Medical Research Council in Great Britain stated[2] that no evidence had been published suggesting that long-term exposure to ionizing radiations leads to a reduction in the expectation of life in man, though there was evidence of some reduction in the expectation of life in animals thus exposed.

The American report was apparently based on a paper by S. Warren.[3] He extracted details of the age and cause of death of medical practitioners from the obituary columns of the *Journal of the American Medical Association*, where these details are regularly recorded, and found that the average age at death of radiologists was 60.5 years, while that for physicians not known to have contact with radiation was 65.7 years. For specialists having some degree of exposure to radiation—for example, gastro-enterologists and urologists—the average age at death was 63.7 years. From this evidence Warren concluded that exposure to ionizing radiation was the predisposing factor in this shortening of life. This conclusion has recently been challenged by E. B. Lewis[4] and by R. Seltser and P. Sartwell.[5] They show that the differences in the age at death can be explained by differences in the age distribution of radiologists and other American physicians. There were proportionately fewer radiologists over the age of 65, and they would therefore be expected to die at a younger average age. In fact, if the age-specific death rates for all physicians at different ages had applied to the population of radiologists their average age at death would have been 58.9 years instead of the observed 60.5 years. The authors

[1] National Research Council, *The Biological Effects of Atomic Radiation*, 1956. Washington.
[2] Medical Research Council, *The Hazards to Man of Nuclear and Allied Radiations*, 1956, Cmd. 9780, H.M.S.O., London.
[3] Warren, S., *J. Amer. med. Ass.*, 1956, **162**, 464.
[4] Lewis, E. B., *Science*, 1957, **125**, 965.
[5] Seltser, R., and Sartwell, P. E., *J. Amer. med. Ass.*, 1958, **166**, 585.
[6] Frost, W. H., *Amer. J. Hyg.*, 1939, **30**, 91.
[7] Case, R. A. M., *Brit. J. prev. soc. Med.*, 1956, **10**, 159.
[8] Dublin, L. I., and Spiegelman, M., *J. Amer. med. Ass.*, 1947, **134**, 1211.
[9] *Registrar-General's Decennial Supplement for England and Wales 1951, Occupational Mortality, Part II*, 1958, **1**, H.M.S.O., London.

of both papers agree that the data are not complete, but there seems little reason to doubt that they have prevented a statistical fallacy from becoming a "recognized fact." They point out, correctly, that their work does not constitute proof that radiologists' exposure to radiation has no effect on their length of life, and suggest that the best evidence of the truth or otherwise of Warren's hypothesis would be obtained by the method of cohort analysis described by W. H. Frost[6] in America and R. A. M. Case,[7] among others, in Great Britain.

Because there is no evidence of a shorter life in radiologists, it does not mean that their mortality from certain diseases is not higher than among other physicians. There is some evidence that American radiologists die of leukaemia more often than other physicians, but the number of deaths is very small. Between 1938 and 1952, according to Lewis, 17 deaths of American radiologists were attributed to leukaemia, with 3.4 expected. It is clear, then, that the problem must not be allowed to get out of perspective. The generality of American physicians also had a greater risk of dying from leukaemia than the population at large.[8]

Evidence from Great Britain is not sufficient to draw any conclusions concerning the deaths of radiologists. An attempt was made by the Registrar-General in his recent Occupational Mortality Supplement,[9] but apart from the comparatively small number of radiologists there was no certainty that they all recorded themselves at census or were registered at death as radiologists rather than under the more general description of medical practitioner. For medical practitioners as a whole it appears from the 1949–53 analysis that their expectation of life is slightly greater than that for all males. There is some evidence, however, that they are more liable to die from leukaemia than other men, but as with the American figures the absolute numbers are very small, and the possible effect of better diagnosis cannot be ruled out. Clearly, all reasonable precautions must be taken to protect radiologists and radiographers from ionizing radiations, and the evidence does not at present indicate any failure to take them.

HAEMOGLOBINS AND NATURAL SELECTION

The discovery of variants of adult haemoglobin in man[1] has been followed by those of haemoglobin variants in animals. Thus H. Harris and F. L. Warren[2] in Great Britain and R. Cabannes and C. Serain[3] in Algiers have found that sheep possess two types of haemoglobin. J. V. Evans and colleagues[4] produced evidence that these haemoglobins were inherited as if they were the products of two allelic genes of which each was responsible for one of the two haemoglobins. Sheep could be homozygous for one or the other of the two haemoglobins, or they could be heterozygous for both. The incidence of the two sheep haemoglobins varied from breed to breed.[5] One sheep haemoglobin denoted by the letter "B" predominated in the lowland breeds, and the other, "A," was much more conspicuous in the mountain and hill breeds. For example, in the Scottish Blackface 61% of the animals were of type A, 33% were AB, and 6% were B. In the South Devon 8% were A, 36% AB, and 56% B; in the English Leicester no type A animals were observed, 2% were AB, and 98% were B.

Up to now the significance of this haemoglobin polymorphism in sheep has been obscure, but some recent work may elucidate it. Professor J. H. P. Jonxis and his collaborators at Groningen University announced on April 26 at a meeting of the Netherlands Association for Haematology in Amsterdam that they had found a difference in the oxygen dissociation curves of the two sheep haemoglobins. The haemoglobin with the greater affinity for oxygen is sheep haemoglobin A (called type II by Professor Jonxis and Dr. Huisman), which Evans and colleagues had found to be more frequent in the mountain breeds. As there is less oxygen in the air at higher altitudes it can readily be understood why in such regions natural selection should have favoured sheep which possess the haemoglobin with the greater affinity for oxygen. A second observation was that the haemoglobin with the lower affinity for oxygen might protect sheep against some of the consequences of anaemia. When individual sheep of the AB type were made anaemic a change could be seen in the proportion of the two haemoglobins. Production of haemoglobin B (type I) was favoured at the expense of that of haemoglobin A. At sea-level, where the oxygen tension of the air is optimal, both sheep haemoglobins can be expected to take up the required amount of oxygen from the air. However, if the haemoglobin content of the blood is decreased because of anaemia it would be an advantage if the oxygen affinity of the haemoglobin was as low as possible, so that relatively more oxygen can be transferred to the tissues. Haemoglobin A would be more useful when there is a need to improve the acquisition of oxygen from the air, and haemoglobin B when it is desirable to facilitate the transfer of oxygen from the blood to the tissues. We have here a good example of balanced polymorphism where individual heterozygotes enjoy advantages over both homozygotes.

Much is known about the differences between human adult and foetal haemoglobins (A and F). Some of the adult haemoglobins have been studied, but only a few results have been published, and they are concerned exclusively with sickle-cell haemoglobin (haemoglobin S). Becklake and colleagues[6] found that the oxygen dissociation curve from four patients with sickle-cell anaemia was displaced to the right—that is, showed less affinity for oxygen than normal blood. However, six of seven bloods from carriers of the sickle-cell trait (haemoglobins A plus S) showed no such change. These observations together with others[7 8] on the oxygen affinity of dialysed solutions of haemoglobins A and S were taken to show that the difference in oxygen affinity of sickle-

[1] *Brit. med. J.*, 1957, **1**, 5.
[2] Harris, H., and Warren, F. L., *Biochem. J.*, 1955, **60**, xxix.
[3] Cabannes, R., and Serain, C., *C.R. Soc. Biol. (Paris)*, 1955, **149**, 1193.
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[6] Becklake, M. R., Griffiths, S. E., McGregor, M., Goldman, H. I., and Schreve, J. P., *J. clin. Invest.*, 1955, **34**, 751.
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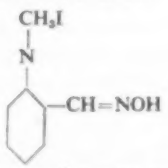
cell anaemia blood was due to some non-haemoglobin dialysable factors. N. D. Fowler and colleagues[9] found that ten patients with sickle-cell anaemia not only had haemoglobin with a lower oxygen affinity, but also had an increased gradient in oxygen tension from alveolar air to arterial blood. However, this can hardly be associated with the sickle-cell haemoglobin directly. These interesting developments in the study of sheep haemoglobins and our inadequate knowledge of oxygenation in the different haemoglobins of adult man should serve to stimulate further investigations into the physiology of the human haemoglobins.

EFFECTIVE THERAPY FOR PARATHION POISONING

In a recent discussion in these columns[1] of the dangers of insecticides reference was made to drugs that could reverse the inhibition of the enzyme cholinesterase caused by poisonous doses of certain organophosphorus compounds. An account in English[2] has now appeared of the Japanese work referred to there. The authors report that over 6,000 cases of poisoning are believed to have resulted from parathion in Japan, and they describe in detail the treatment of three serious cases of parathion poisoning in which the symptoms were dramatically relieved by an intravenous injection of 1 g. of 2-pyridine aldoxime methiodide (P.A.M.) as a 5% solution in water. Its structural formula is as follows:



Within a few minutes consciousness returned, muscular fasciculations ceased, the blood pressure fell, and other symptoms rapidly receded. The effects appear to have been maintained and no undesirable side reactions followed this dose of P.A.M. The rapid return of consciousness is interesting because P.A.M., being a quaternary compound, would not be expected to penetrate the blood–brain barrier. Coma may therefore be secondary to the asphyxia rather than a result of inhibition of the brain cholinesterase by the insecticide. P.A.M. can be purchased commercially in Great Britain, and it would be worth making supplies available to dispensers for doctors in areas where cases of parathion poisoning may arise.

D. Grob and R. J. Johns[3] have also described the effect of P.A.M. and another oxime, diacetyl monoxime, on the muscle responses in normal and myasthenic patients given several different anticholinesterases. They did not observe such dramatic reversal of the toxic effects, but parathion was not included among the anticholinesterases injected. It is established that the action of these oximes in reversing inhibition of cholinesterase does vary with the different inhibitors used.[4] Since injection of P.A.M. appears to have no untoward effects, it could be tried in a severe case of poisoning by any of the organophosphorus insecticides, but it is possible that the striking results recorded by the Japanese workers may not necessarily be seen in victims of poisoning by some of the other very toxic anticholinesterases. However, on current theories it is reasonable to predict that treatment with P.A.M. would be as effective in cases of poisoning by an organophosphorus compound with a diethoxyphosphate moiety, such as amiton or T.E.P.P., as in poisoning by parathion.

[1] *Brit. med. J.*, 1958, **1**, 989.
[2] Namba, T., and Hiraki, K., *J. Amer. med. Ass.*, 1958, **166**, 1834.
[3] Grob, D., and Johns, R. J., *ibid.*, 1958, **166**, 1855.
[4] Childs, A. F., Davies, D. R., Green, A. L., and Rutland, J. P., *Brit. J. Pharmacol.*, 1955, **10**, 462.

POLIOMYELITIS VACCINE

Earlier this spring the scheme for vaccinating children and others in the priority classes against poliomyelitis ran into difficulties. For the reasons we outlined in last week's *Journal*[1] the chances of completing by June 30 the immunization of all those already registered seemed to be becoming remote. But a decision made last week by the Minister of Health, and announced in Parliament (see p. 1128), should quicken the progress of the scheme. Guided by the advice of the Medical Research Council, the Minister will allow, as a temporary measure, Canadian and American vaccine to be issued for use without prior submission to British tests. But the vaccine must have been tested and licensed for use in its country of origin. Thus vaccine now ordered from the U.S.A. and Canada need not go through the time-consuming "check-tests" to which transatlantic vaccine has up till now been submitted by the Medical Research Council. This should enable the gap in supplies of vaccine to local health authorities to be quickly filled, but it remains to be seen whether parents will readily accept the offer of immunization by Salk vaccine not tested in this country. The Medical Research Council's recent statement on poliomyelitis vaccines is published at p. 1117 in this issue. It is a straightforward and logical explanation of what led the Medical Research Council to give the Minister the advice it did. The safest poliomyelitis vaccine known is that made according to the British formula and tested by the British tests, and "preference should always be for the safest known vaccine." Therefore the statement stresses that "the role of imported vaccine untested in this country should be limited to that of a temporary supplement to meet the present shortage." Further, the final aim should be to dispense with the need to use any vaccine containing the Mahoney strain. According to the Minister's speech in Parliament on May 1 medical officers of health should receive full information about the new arrangements this week and family doctors are to be sent copies of the Medical Research Council's statement so that they can answer parents' questions about the vaccine.

Meanwhile the National Fund for Poliomyelitis Research, which works in close co-operation with the

[1] *Brit. med. J.*, 1958, **1**, 1053.
[2] *The Times*, May 1.
[3] Dane, D. S., *et al.*, *Brit. med. J.*, 1957, **1**, 59.

Medical Research Council, has launched an appeal for £500,000 to enable "research workers in the United Kingdom to solve the outstanding problems of poliomyelitis."[2] Apart from the need to support further work on improving the killed vaccine now in general use, there is much more research to be done on live virus vaccines. The Fund has already helped to meet the expenses of the work being done with live vaccine by Professor G. W. A. Dick and his colleagues[3] at Queen's University, Belfast, and this research is being continued. The fund also proposes to give financial support to research on orthopaedic treatment and rehabilitation and on the respiratory problems of poliomyelitis.

OESTROGENS AND BREAST CANCER

It is generally accepted that the beneficial effects of oophorectomy and of adrenalectomy in the treatment of patients with metastasizing carcinoma of the breast are primarily due to the removal of ovarian and of adrenal oestrogens.[4 5] Not more than 50% of these patients, those with so-called hormone-dependent tumours, receive benefit. This selective response is one of the main problems of the endocrine therapy of breast cancer.

R. E. Wilson, A. G. Jessiman, and F. D. Moore[6] have recently reported from Boston three patients whose carcinomatosis was exacerbated by oophorectomy, and one patient who responded to oophorectomy but was worsened by subsequent adrenalectomy; these patients were all at about menopausal age. This course of events has not been reported before in any series of cases of oophorectomy or adrenalectomy from other centres.[5 7 8] The authors' procedure of measuring excretion of urinary calcium with their patients on a constant low-calcium intake makes it easier to detect sudden exacerbations by finding an increased urinary calcium; but their method is applicable only to patients with osteolytic skeletal metastases. The adrenalectomized patient, and two of the oophorectomized patients, showed an increase in excretion of urinary oestrogens which was parallel with the exacerbation of the disease, and the authors state that their analytical method for oestrogens is sufficiently sensitive and specific for these results to be significant. The excretion of urinary oestrogens after adrenalectomy + oophorectomy, from dietary sources, other steroids, or microscopical accessory adrenal mesenchymal tissue, has also been reported elsewhere, but could not be correlated with clinical changes.[9]

The beneficial effects of hypophysectomy in the treatment of metastasizing carcinoma of the breast are usually considered to be due to removal of the pituitary stimulus for ovarian and adrenal oestrogens, and also of the pituitary hormones somatotrophin, and probably prolactin,[11] which directly stimulate the breast carcinoma. In general, increased secretion of pituitary trophic hormones follows the removal of control by peripheral hormones, such as by ablation of target glands. The authors reasonably postulate such a mechanism in their patients—namely, that the operation removed oestrogen control of the pituitary gland, which either directly, or indirectly via adrenal tissue, then increased its stimulatory activity on the carcinoma. However, it may be necessary to set against this the claim that pituitary prolactin secretion is stimulated by oestrogens.[11 12] The validity of their hypothesis gains support from the improvement in two of these patients by cortisone suppression therapy, and from improvement in one and transient amelioration in two after subsequent hypophysectomy. Nor has such exacerbation been reported in any series of patients submitted to hypophysectomy.[13–15]

It may be hoped that these interesting observations will prompt further reports of exacerbations occurring after oophorectomy or adrenalectomy, with more detailed direct studies of pituitary function than were possible here. Further investigation is also required of methods that might assess rapid spread of metastatic tumours which are neither osteolytic nor involving the liver, such as the study of changes in serum glycoproteins or in serum phosphohexose isomerase.[16 17]

ARMY PSYCHIATRIC DISCHARGES

Psychiatric reasons loom large among the causes of medical discharge from the Army, especially the discharge of recruits during selection procedure. The 1954[1] report of the Director-General, Army Medical Services, which is the latest to appear, comments. "It is perhaps disturbing that psychiatric conditions were responsible for nearly half the total discharges [of recruits] on medical grounds." The actual numbers are small: out of 8.33 medical discharges per 1,000 intake, 3.48 were for psychiatric reasons. Much the commonest diagnosis was psychoneurosis, accounting for three-quarters of these discharges. The discharge rate for men from the Army as a whole on psychiatric grounds was 4.4 per 1,000 on strength (a figure that includes some which were discharged during selection procedure). By contrast, the discharge rate for women was 19.4. In the categories listed in the report, mental deficiency was equally common in women as men, but discharge for schizophrenia was twice as common in women, anxiety neurosis five times, disorders of character five times, and hysteria six times as common. Discharge rates for all organic diseases taken together were about twice as high for women as for men.

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THE SAFETY OF VINYL ETHER

BY

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In the absence of any information about the number of times any particular anaesthetic is administered it is impossible to evaluate its mortality rate in conjunction with the tables of deaths occurring under anaesthesia issued annually by the Registrar-General of England and Wales and of Scotland. In any given operation there are many variable factors present which may influence the ultimate result: the skill of the surgeon, anaesthetist, and nursing staff; the physical condition of the patient; and the risk carried by the particular operation performed. If a fatality occurs it is extremely difficult, in the absence of any gross error, to apportion the blame. Also, it is usual for the anaesthetist to give several different anaesthetic drugs to each case. When the Ministry of Health carried out its survey of explosion risk in 1954, a table was published showing the frequency of use of each anaesthetic drug, and it was found that on the average 2.4 different drugs were used for each operation performed. But this survey covered only the hospitals of England and did not include anaesthetics given in clinics, in nursing-homes, and in general practice. From this table can be drawn some interesting comparisons of the various anaesthetics given in different types of hospital, but that is all.

Examination of the tables of mortality issued by the Registrars-General also shows that many combinations of anaesthetic drugs are used in major surgery; but in minor surgery it is quite usual to employ only one drug to provide the short period of anaesthesia required. In a short operation, too, the skill of the surgeon and that of the nursing staff are not of such paramount importance as they are in major surgery; while the patient is usually an out-patient well enough to be able to attend hospital. All this makes the responsibility of the anaesthetist even greater, and it behoves him to use the safest possible anaesthetic for the operation. The anaesthetic drugs in common use for minor surgery are nitrous oxide, thiopentone, hexobarbitone, trichlorethylene, ethyl chloride, and vinyl ether. The number of times these anaesthetics are given singly is unknown, with the exception of vinyl ether. Thanks to the courtesy of the sole manufacturers of vinyl ether ("vinesthene") the number of ampoules issued for single-dose anaesthesia each year is known.

During the last ten years 521,800 ampoules of 3 ml. and 5 ml. were issued, and during the same ten years there has been only one death where vinyl ether was the sole anaesthetic. It may be argued that occasionally more than one ampoule is used for a single case. But against this may be set the fact that vinyl ether is also issued in 25-ml. bottles and it is possible to give several short inductions from one bottle. The number of times this occurs it is impossible to estimate, but it is likely to make up for the number of cases which ought to be subtracted from the total number because more than one ampoule has been used.

Side-effects

Vinyl ether was introduced as an anaesthetic by Gelfan and Bell in 1933. The preliminary favourable reports were somewhat modified by the occurrence of five cases of acute yellow atrophy of the liver. In each case more than 300 ml. had been given and the operation had lasted for more than one and a half hours. Since 1941 no other case has been reported, but in most textbooks the reservation has been made that the drug should not be given for longer than half an hour. In my experience it has been given on many occasions for over three hours without untoward sequelae, but the total amount used has never exceeded 200 ml. Convulsions occurring under vinyl ether were encountered (Dawkins, 1940). These convulsions were of two distinct types. One variety took place under deep anaesthesia with soda-lime absorption, the incidence being about 1 in 40. The other type made its appearance during the recovery period following a single dose of vinyl ether for dental extraction. This has an incidence of about 1 in 400, but as there has never been a report of a fatal case the aetiology of these complications must remain obscure. No other side-effects of vinyl ether anaesthesia are known.

Comparison with Ethyl Chloride

It is surprising that an anaesthetic with such a high degree of safety is not more widely used. It may be objected that it is extremely volatile and so difficult to give; that it decomposes rapidly when exposed to air, and so must be used within 24 hours of opening the container; that it is rather expensive; and that the garlic-like smell is unpleasant. But the safety of the drug should outweigh these disadvantages. The drug most often used for short anaesthesias in young children is ethyl chloride, but the phrase coined about ethyl chloride, "dead easy—easy dead," is all too apt. This anaesthetic has many serious disadvantages. It is so toxic that only one dose may be given. If an overdose is given the respiratory centre and the cardiac centre are likely to fail together; there is no safety margin as there is in all other anaesthetics except chloroform. With an impending overdose, spasm of the masseter is common, so that it is very difficult to open the mouth to pull the tongue forward. Involuntary micturition during anaesthesia is also common.

None of these complications is encountered with vinyl ether. Ethyl chloride is, of course, widely used in this country by anaesthetists who are trained to overcome its dangers, but it is best avoided by the occasional anaesthetist. It is perhaps significant that in one hospital in the U.S.A. the use of ethyl chloride by a resident results in instant dismissal; while in others a form accepting all responsibility in the event of a fatality has to be signed before its use.

It has been shown (Jarman, 1939) that deaths from anaesthetics could be classified into three groups according to the experience of the administrator. If anaesthetists in training, whose skill is difficult to assess, are excluded, in 80% of deaths the administrator was a newly qualified houseman, in 12% a general practitioner, and in 8% a consultant anaesthetist. But, although striking, these figures are not very much use in the absence of information about the numbers of anaesthetics given by each class. In recent years, with the increased number of anaesthetists, trained or in training, available, it has become more rare for newly qualified housemen to be asked to give an anaesthetic. And if they do give one they may, as a recent case has shown, find themselves in court accused of negligence. Therefore, if a houseman has to give an anaesthetic for a minor operation, he should use that which is safest. The mortality from ethyl chloride is unknown, as it is impossible to ascertain the number of times it is given, but the Ministry of Health tables show that it was given six and a half times more often than vinyl ether. During the last ten years there have been 69 deaths under anaesthesia where ethyl chloride was the sole anaesthetic—and one with vinyl ether.

Deaths under Various Anaesthetics

For the sake of comparison with the other anaesthetics used in minor surgery, the numbers of deaths under each

anaesthetic in England, Wales, and Scotland during 1947–56 are shown. They were:

Nitrous oxide	350	Trichlorethylene	15
Thiopentone	792	Ethyl chloride	69
Hexobarbitone	13	Vinyl ether	1

Where the anaesthesia was prolonged by the addition of nitrous oxide and oxygen the figures were:

Nitrous oxide and trichlorethylene	118
,, ,, ,, thiopentone	407
,, ,, ,, hexobarbitone	3
,, ,, ,, ethyl chloride	57
,, ,, ,, vinyl ether	0

In the absence of information on how often each anaesthetic was given it is unwise to draw any conclusion, but in the case of vinyl ether it has been shown that the mortality is less than 1 in 500,000.

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VACCINES AGAINST POLIOMYELITIS

STATEMENT BY MEDICAL RESEARCH COUNCIL ON THE CURRENT POSITION, APRIL 29, 1958

This statement was issued by the Medical Research Council immediately after the Minister of Health's speech in the debate in the House of Commons on May 1 on supplies of poliomyelitis vaccine (see p. 1128).

1. The Medical Research Council have been asked by the Government to advise whether, in view of the present shortage of poliomyelitis vaccine, American or Canadian Salk vaccine which has satisfactorily passed safety tests and been licensed for issue in the country of origin should be made available for use in this country without first being subjected to the safety tests of the Medical Research Council.

2. The Council have made a full review of the current situation in the light of their responsibilities for safety testing poliomyelitis vaccine in this country. They have given careful consideration to all the available evidence on the risks attending the use of the various poliomyelitis vaccines now being produced; on the risks in different circumstances of leaving a large number of children and others in special need of protection unvaccinated during the late spring and early summer months of this year; and to information on the amount of vaccine likely, under present arrangements, to become available for use in the next few months.

Vaccines Available

3. Three vaccines against poliomyelitis are available for consideration: the British vaccine; imported American or Canadian vaccine that has passed British safety tests; and imported vaccine from the American or Canadian sources that has not been subjected to British safety tests. The two former are now in use in this country; the latter, at present, is not, although vaccine of this type has been used extensively elsewhere.

4. All poliomyelitis vaccine at present in use is made from three types of virus, types I, II, and III. In both the British and the American or Canadian vaccines, similar strains of the type II and type III viruses are used. On the other hand, two different strains of type I virus are used. The American and Canadian vaccines include the relatively virulent type I strain, known as Mahoney; the British vaccine, the much less virulent type I strain, known as Brunenders. If, therefore, some of the virus failed to be inactivated in the course of manufacture, the British vaccine would be less likely to produce poliomyelitis on injection than would vaccines made from the Mahoney strain.

It is the use of a type I strain of low virulence that makes the British vaccine the safest yet produced.

5. All vaccines are submitted to a series of safety tests at several stages before issue, both during and after manufacture, with the object of detecting any virus that has survived the process of inactivation. Of necessity only samples of each batch of vaccine can be tested, and the possibility inevitably remains that in the untested part of the batch a few particles of live virus may still be present. It follows, therefore, that the greater the size and number of the samples tested, the smaller is the chance of any surviving virus remaining undetected and the greater the assurance that can be given regarding the safety of the vaccine.

6. If vaccine is submitted to an adequate number of safety tests of the full range now in use, there is little chance of contamination with live virus escaping detection. If a few particles of live virus do escape, the effect on the safety of the vaccine will depend upon their virulence. With the Brunenders strain of relatively low virulence used in the British vaccine, it is most improbable that any ill effects would follow inoculation; with the Mahoney strain, used in the American and Canadian vaccines, such a possibility could not be excluded with the same assurance.

7. It was because the more virulent Mahoney strain is used in the preparation of American and Canadian vaccine that the Medical Research Council, when recommending that vaccine should be imported from these countries to meet the shortage of poliomyelitis vaccine in the summer of 1957, linked that recommendation with the proviso that such vaccine should be submitted to further safety testing in this country in order to increase the safeguards against any particle of live virus of the virulent strain being present in the vaccine when issued.

Order of Safety

8. Taking all these factors into account, the Medical Research Council believe that the three vaccines under consideration can be placed in the following order of safety:

(*a*) Vaccine made according to the British formula that has successfully passed British safety tests.

(*b*) Imported vaccine from America and Canada that has successfully passed safety tests in the country of origin and also British safety tests.

(*c*) Imported vaccine from the same sources that has successfully passed safety tests and been licensed for issue in the country of origin.

9. After carefully weighing all the available evidence bearing on this complex problem, the Council are satisfied that the risk of producing paralytic poliomyelitis by injecting any one of these three vaccines is very slight and that a person inoculated with any one of them is substantially less likely to contract paralytic poliomyelitis than if he is left uninoculated. Nevertheless, no vaccine can be guaranteed to be wholly free from risk, and the preference should always be for the safest known vaccine.

10. The Council reaffirm their view that British-type vaccine which has successfully passed British safety tests is the safest poliomyelitis vaccine known; that the only justifiable permanent policy is to use every endeavour to produce this in such quantities as to meet all the needs of this country; and that any policy which has recourse to less safe vaccines should, however slight the risk, only be regarded as temporary.

Next in order of preference is imported vaccine that has passed successfully British safety tests as well as tests in the country of origin.

Third is imported vaccine which, although it has successfully passed safety tests in the country of origin, has not been submitted to the further British tests carried out by the Medical Research Council in this country.

Recommendations

11. The present problem arises because supplies of British vaccine and imported vaccine that have passed British safety tests are together insufficient to meet requirements, and cannot become sufficient in time to prevent a substantial deficit during the summer months when the incidence of poliomyelitis may be expected to increase.

12. After carefully examining the present situation the Medical Research Council have concluded that, as it would

appear to be impossible to overcome by any other means the deficit which will otherwise be inevitable during the summer months, it would be advisable as a temporary measure to issue American or Canadian vaccine which has not been submitted to British tests, provided that it has been tested and licensed for use in the country of origin.

13. In proffering this opinion, however, the Medical Research Council wish to stress their advice that the role of imported vaccine untested in this country should be limited to that of a temporary supplement to meet the present shortage. At the same time every endeavour should be made to obtain the maximum possible supplies of British vaccine and imported vaccine which has satisfied both British tests and tests in the country of origin, so that, at the earliest possible moment, the need to use imported vaccine untested in this country will disappear. The final aim should be to dispense with the need to use any vaccine containing the Mahoney strain.

IMPERIAL CANCER RESEARCH FUND

FINANCE AND RESEARCH

Last year the Imperial Cancer Research Fund spent nearly £125,000 on research and the maintenance of its laboratories.* Receipts showed a very satisfactory rise, thanks to the generous response from subscribers and certain firms to a special appeal for the building of the proposed new laboratories on the site of Nos. 44–46, Lincoln's Inn Fields (see *Journal*, May 3, p. 1075): subscriptions and donations rose by £55,673 to £122,408; dividends by £2,387 to £56,446; and legacies by £41,092 to £229,660. Nevertheless so far only one-third of the sum needed to build the new laboratories has been collected: a further £600,000 is wanted this year. Administration and appeals cost 1s. 2d. in the pound last year. The Jack Buchanan memorial fund raised £14,000.

Research

The Fund's research is carried out in two distinct sets of laboratories. At Mill Hill, under the direction of Dr. JAMES CRAIGIE, F.R.S., the work is largely concerned with tumour growth in animals and the biological characteristics of malignant tumours. Among other studies there, human growths are being transplanted to animal hosts. Variations in the rate of tumour growth after transplantation have been observed, and it is hoped by manipulating the environment of these transplanted tumours to throw some light on the question of acquired immunity. At No. 48, Lincoln's Inn Fields, Professor GEOFFREY HADFIELD is directing research, in co-operation with the staffs of certain London and provincial hospitals, on the hormonal control of cancer in man, particularly cancer of the breast and prostate. Other work concerns cytological diagnosis.

Dr. Craigie is investigating an unexpected finding of reduced resistance in mice to a second inoculation with carcinoma 63; usually the second implant regresses more rapidly than the first. Mr. P. C. Williams and Dr. D. J. Trevan are studying experimentally the kidney lesions which result from stilboestrol therapy. Dr. F. C. Chesterman has been applying techniques learnt at the Sloan-Kettering Institute, New York, to the heterotransplantation of human lung cancer. Professor Hadfield and Dr. Stretton Young have been studying the pituitary control of breast tissue. They have identified a substance in the serum of women which is probably the same as the mammatrophic agent found in the urine of normal women. Their results strongly suggest that this agent is not a steroid hormone and that it originates from the anterior pituitary. Dr. J. Bamforth is testing the reliability of cytological diagnosis in cancer of the cervix, prostate, and lung. He reports: "It is already justifiable to say that exfoliative cytology provides sound evidence of carcinoma of the uterine cervix before the naked-eye lesion has become typical." Dr. L. M. Franks has continued his clinico-pathological studies of the biological activity of human prostatic cancers, and the effects on them of endocrine treatment. Drs. R. D. Bulbrook and F. C. Greenwood have been comparing the response to treatment of breast and prostatic cancer with the level of urinary excretion of oestrogens. Finally, Professor G. J. Cunningham, at the laboratories of the Royal College of Surgeons, is attempting to assess the clinical significance of histological abnormalities in human lung.

Imperial Cancer Research Fund: Fifty-fifth Annual Report, 1956–1957, April, 1958.

ROYAL SOCIETY OF HEALTH

CONGRESS AT EASTBOURNE

Well over 2,000 delegates attended the Royal Society of Health's annual congress, which was held at Eastbourne from April 28 to May 2. Disappointingly the Minister of Health could not attend the opening personally, and instead the chairman of the Society's council, Dr. JOHN A. SCOTT, invited Mr. R. THOMPSON, Parliamentary Secretary to the Ministry, to read the Minister's address.

Minister's Address

After a passing reference to the ideal health service which would actively promote physical and mental fitness and thus reduce disease and accident, Mr. D. WALKER-SMITH discussed what he described as certain major problems on our plate. These were the sheer pressure of population and the inexorably increasing proportion of the elderly; mental health; the prevention of accidents in the home, particularly burns and scalds, which caused over 800 deaths a year, and education of the public about the relationship between smoking and lung cancer; and, lastly, the prevention of dental caries by fluoridation and in other ways.

Smoking as a subject of health education was new, he said, and undoubtedly more difficult than many of the past measures that health workers had been called upon to advocate. The Medical Research Council had established as reasonable a connexion between smoking, particularly heavy smoking of cigarettes, and cancer of the lung. As with any other hazard to health which could be avoided by personal action, it became a part of the responsibility of the Ministry of Health and the local health authorities to make the public aware of the hazards and what could be done to avoid them. There were difficulties to overcome, however; the subject was still one of controversy, even though the facts could not be denied. Nevertheless, said the Minister, the authorities had set about this new challenge with a will.

After the inaugural session the Congress broke up into its twelve sections and four conferences to discuss various specialized aspects of the public health. Among the major debates were symposia on the Report of the Royal Commission on Mental Illness, epidemic influenza, the epidemiology of non-infectious diseases, the needs of the elderly, fatigue, and the role of the out-patient department.

Conference of M.O.H.s

For his presidential address to the Conference of Medical Officers of Health Dr. H. D. CHALKE, president of the Society of Medical Officers of Health, discussed the "new public health" of this age of nuclear fission, electronics, automation, and speed. The popular press could give much help, he said, if it would not over-emphasize and sensationalize its medical news; so could television were it not for its quite extraordinary devotion to disease rather than its prevention. The new public health recognized the fundamental position of the family: "fireside happiness" was the best purveyor of mental health.

After this the Conference of M.O.H.s proceeded to discuss the epidemiology of non-infectious diseases. Dr. R. E. HOPE SIMPSON, who spoke on upper respiratory diseases, pointed out that the common cold, as an example of a non-notifiable disease, plagued the average person for 700 out of the

(*Continued on p. 1119*)

To-day's Drugs

Under this heading we hope to publish from time to time authoritative notes on a selection of new drugs.

Romilar Syrup and Tablets (Roche Products Ltd.).—Romilar is a cough suppressant, containing dextromethorphan, the dextro-isomer of 3-methoxy-N-methylmorphinan. It has been shown in careful double-blind studies to be an effective substance for this purpose, about equal in potency to codeine. Methorphan is a synthetic substance related to the powerful analgesic "dromoran" (3-hydroxy-N-methylmorphinan), to which it bears the same relationship as codeine bears to morphine. The dextro-isomer (like that of dromoran) has, however, been shown to have little or none of the central depressant, analgesic, and addictive properties possessed by the laevo-isomers and by codeine. Dextromethorphan is reported to have produced very few side-effects and no addiction. It is registered as a First Schedule poison. 15 to 30 mg. (1–2 tablets or teaspoonfuls) may be given up to four times daily.

(*Continued from p. 1118*)

3,500 expected weeks of his life, compared with measles's one or two weeks. The humidity and temperature of the air appeared to influence the morbidity rate. Dr. M. J. PLEYDELL described his epidemiological studies in Northamptonshire of Huntington's. chorea, mongolism, anencephaly, and congenital heart disease. Dr. S. L. MORRISON spoke on the incidence and distribution of psychotic illness.

Preventive Medicine

Sir KENNETH COWAN, C.M.O., Department of Health for Scotland, gave the presidential address to the Section of Preventive Medicine, whose subject was epidemic influenza. He referred to the way epidemic diseases waxed and waned over the centuries, a periodicity which was not understood and whose full implications were not apparent even to-day. In the Western world the scope of the epidemiological method must now be widened to include mass disease or trauma. A combination of intensive epidemiological study with the application of public health methods could make a great impact on many conditions such as coronary disease and various forms of cancer which had become urgent public health problems.

Dr. C. H. ANDREWES, F.R.S., opened the symposium on epidemic influenza. The recent epidemic had differed from many of its predecessors in the speed with which it had spread right across the world in six months and in its very good press, which had aroused more alarm than its severity would justify. Influenza was able to afflict adults many times over because it attacked a mucous surface where antibodies from previous attacks were not readily available and because the virus kept changing its antigenic make-up.

Other Speakers

The presidential address to the World Health Section was given by Sir JOHN CHARLES, C.M.O., Ministry of Health, and he described the broadening vistas of the World Health Organization's programmes. Sir ARTHUR MASSEY, C.M.O., Ministry of Pensions and National Insurance, in his presidential address to the Section of Health and Welfare of the Family, introduced the subject of the welfare of the elderly, which the Section then debated.

Other presidential addresses were given by Dr. R. F. TREDGOLD (Section of Mental Health) and by Sir JAMES KILPATRICK (Section of Tropical Hygiene); Mr. K. I. JULIAN, the chairman of the South-east Metropolitan Hospital Board, addressed the Hospitals Section, and Sir HUGH BEAVER the Section of Occupational Health. Professor ALAN MONCRIEFF was president of the Section of Health Education, which, after his presidential address, discussed dental disease—"the last great epidemic."

Correspondence

Management of Respiratory Paralysis

SIR,—I have read the article by Dr. John A. Forbes "Management of Respiratory Paralysis using a 'Mechanical Cough' Respirator" (*Journal*, April 5, p. 798) with considerable interest. On various points, however, I think a few comments are needed.

It opens with the statement that "pulmonary disease has been a major contributing factor to deaths among patients undergoing prolonged artificial respiration." This may be so in patients being ventilated in tank respirators over long periods of time, but is certainly not the case when intratracheal positive-pressure is used. In such patients, having survived the first months after the acute stage, death from pulmonary complications is a rare exception—a point, it seems, in favour of intratracheal positive-pressure ventilation. In the discussion the author enumerates the reasons why tank respiration has been retained as the basic method in his hospital. This being the case, he must have been very fortunate indeed in regard to the severity of the patients who have come under his care. But why at all have a "basic method," because the methods to choose always depend on the symptomatology of the individual case? If the patient can be pulled through using the more conservative methods—i.e., the tank, with the patient in a drainage position—they should be used. But if, on the other hand, these methods do not produce adequate aeration of the blood, a tracheotomy often followed by intratracheal positive-pressure ventilation becomes necessary. There is simply no choice.

From a few published figures—three in all—on mortality amongst acute polio patients with respiratory failure (see his Table IV) the author draws the conclusion that fatality rates are lower with tank respiration than with intratracheal positive-pressure ventilation. It is true that the average mortality in 1952 in our acute patients with respiratory failure, etc., was higher than the tank results quoted from San Francisco and Melbourne. But the author forgets to mention three quite decisive points which deprive this comparison of methods of all scientific value:

(1) During the acute stage we worked against very disadvantageous odds: inadequate equipment and an overwhelming number of patients. This of course stamped its mark on indications as well as on results.

(2) The author seems to have overlooked the fact that the results steadily became better during the course of the epidemic, despite its unabating severity. During the last months of the year fatality rates came down to figures comparable to the tank results quoted.

(3) The author has not attempted to group the materials cited according to clinical severity, which is *the* crucial point when trying to compare therapeutic results.

In our book[1] fatality rates are listed in relation to severity of the disease. The table shows an exceptionally large number of very grave cases, mortalities ranging from 25 to 85%, closely correlated to the severity of the disease. The extraordinary severity of the epidemic is borne out by the fact that between 25 and 50% of the 1,250 paralytic cases had impairment of respiration necessitating special therapeutic measures. As already said, comparison of therapeutic results is worthless unless correlated to a specified and reproducible classification of cases. Just one point more. Dr. Forbes states that "the dangers of circulatory changes as the result of unopposed intratracheal positive pressure . . . do not arise" when the tank is used. The tank respirator being a positive-pressure machine, this statement—without further details—does not seem convincing, to say the least.

In our opinion the advantages of intratracheal positive-pressure ventilation over tank ventilation in polio patients with *chronic* respiratory insufficiency far outweigh the few disadvantages. Our chronic patients are sitting up in their wheel-chairs the greater part of the day while the tank patients are encased in a narrow metal box with the head sticking out through a diaphragm. If the extremities have retained some muscular force the patient cannot use them in the tank, while our patients can make the best of every

residual muscular power—knitting, writing, playing games, etc. In the tank, physiotherapy has to be abandoned more or less and nursing is more cumbersome. May I add that the morale of our chronic polio patients being ventilated by intratracheal positive-pressure since 1952 is excellent, a fact which has impressed everybody visiting our hospital?—I am, etc.,

Copenhagen. H. C. A. LASSEN.

REFERENCE

[1] Lassen, H. C. A., *Management of Life-threatening Poliomyelitis, Copenhagen, 1952-6*, Edinburgh, 1956.

SIR,—I have read with interest Dr. J. A. Forbes's article on the management of respiratory paralysis (*Journal*, April 5, p. 798), though his enthusiasm for the tank respirator, even for patients requiring tracheotomy, is not shared by those with experience of positive pressure respiration in this country.

I must, however, correct his assumption that positive pressure respiration produces "dangers of circulatory changes" and tank respirators do not. This fallacy, which is lamentably widespread, stems from a failure to appreciate that in both methods the intrathoracic pressure is raised above the pressure on the surface of the body and therefore tends to impede venous return to the heart. Bower,[1] whom Dr. Forbes quotes in another connexion, explains this at more length and should be consulted by anyone who is still in doubt.—I am, etc.,

Oxford LIONEL H. OPIE.

REFERENCE

[1] Bower, A. G., *Diagnosis and Treatment of the Acute Phase of Poliomyelitis*, 1954, Williams and Wilkins, Baltimore.

Dirty Habits

SIR,—If anyone wants confirmation of Dr. Jno. Crawford's remarks (*Journal*, April 19, p. 943) on dirty habits I suggest that first-class railway toilets will provide it. I travel once or twice a month between London and Crewe. The toilets are in frequent use, no one on a railway journey is pressed for time, and washing facilities are immediately available and adequate. On the way to Euston, in a morning, I notice that there is usually quite a pile of used paper towels by the time we reach London, so hands are probably washed relatively frequently after the morning defaecation: but on the return journey at night I have noticed that frequently there are very few used paper towels by the time I get to Crewe, even on a full train, so that washing after micturition is probably very infrequent and so is washing before dinner on the train. From the unused look of the two soap tablets provided it would seem that most people are content with just swilling their hands instead of washing them.

But all this just goes to show how relatively rare infections are from this cause. The natural secretion of the hands is bactericidal to many pathogenic cocci, but I do not know whether it is so to the enteric group, and a wise and cleanly person will take all precautions.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

SIR,—I was most interested to read Dr. Jno. Crawford's letter on dirty habits (*Journal*, April 19, p. 943). It prompted me to reflect somewhat ironically, and not without nausea, on the very evil-smelling and thoroughly unhygienic public conveniences in various parts of the country. The worst I have yet had the misfortune to experience was situated at a recognized stop on the Edinburgh to London express coach service. Here the smell was so foul that many refrained from eating in the adjoining dining-room.

Surely it must be possible to educate the population in hygiene? Perhaps the television services might do good in this respect rather than pandering to the morbid curiosity of certain members of the public.—I am, etc.,

Edinburgh, 4. J. K. STUART BELL,
Medical Student.

SIR,—I read with interest Dr. Jno. Crawford's letter on dirty habits (*Journal*, April 19, p. 943). I wondered how many of the persons he observed as a ship's surgeon were medical men or women. I raise this question because quite recently I have been witness to a dirty habit practised by two general practitioners who visited my children during a recent influenzal epidemic. One of these, in particular, is an excellent general practitioner, and I have every confidence in his diagnostic and therapeutic ability. However, to my wife's horror, after inserting a clinical thermometer in the mouth of one of my children and registering a temperature of 101° F. (38.3° C.), he replaced this instrument into its metal case without even asking for water or a cloth with which to wipe it. Presumably, if he would do this in a doctor's house, he was visiting others in the district and perpetrating this inexcusably dirty, dangerous, and pernicious habit on others.

For obvious reasons, I sign myself as

DOCTOR.

Tuberculous Pleural Effusion

SIR,—I was interested to read the letter of Drs. John Mackay-Dick and David Slattery (*Journal*, April 12, p. 888) concerning the treatment of tuberculous pleural effusions. Their methods seem praiseworthy in their thoroughness. In my own experience I have never found that complete aspiration with streptomycin replacement has any untoward effect in the early acute stages, though always in European patients. While I would certainly recognize that "at least 18 to 24 months of chemotherapy" should avert any subsequent development of more serious tuberculosis, and should support similar assertions in post-primary tuberculosis of the lung, it is at least open to question whether such long periods are necessary in primary tuberculous pleural effusions without obvious parenchymal involvement.

There have been four papers which have tried to analyse the effect of short-term chemotherapy upon late complications of tuberculous effusions.[1-4] Subsequent tuberculous manifestations were found in from 4 to 8% of each series, despite chemotherapy of up to six months' duration. This compares to an expected 20–30% relapse when cases are treated without chemotherapy.[1 2] These papers, including my own, are all open to criticism for differing reasons, but at least show that short-term chemotherapy has largely, but not completely, eliminated subsequent tuberculosis. What is needed now is either a controlled series of cases treated by chemotherapy for varying longer periods, such as 6, 12, and 18 months; or a survey of the effect of longer chemotherapy upon such cases in a community of moderate size, comparing the results with the expected rate of tuberculous complications if chemotherapy had not been used, as defined above.

The controlled series would be impracticable nowadays in Britain, mainly because tuberculous pleural effusions have become uncommon: Drs. Mackay-Dick and Slattery may have a more suitable population in Malaya for such a trial. It would also be unethical to treat such patients without chemotherapy, in view of the results detailed above. The community survey, although less ideal, and also retrospective, would at least indicate the impact of chemotherapy upon the breakdown rate of subsequent tuberculosis in the whole local population.

I have had perforce to adopt something after the second method in a study that a colleague and I have just made. We have tried to find how many patients with primary tuberculous pleural effusions have developed further tuberculous manifestations despite chemotherapy during the years 1953, 1954, and 1955 in the City of Edinburgh. We have studied all the cases satisfying our criteria that we were able to find in hospital records, giving some picture of the problem as a whole, though necessarily an incomplete one. Preliminary assessment indicates that of 14 patients treated with less than six months of chemotherapy, only one (7%) developed further tuberculosis. Of nearly 70 treated with longer periods of chemotherapy, mainly 9 to 12 months, all have remained well and free from disease. No patients have eluded the follow-up. These results will be discussed in a paper to be submitted for publication.

It appears that 9 to 12 months of chemotherapy should be sufficient to prevent subsequent tuberculous manifestations

in the great majority of patients with primary tuberculous pleural effusions, without obvious parenchymal involvement. Presumably the bacilli are readily accessible and their total population not very large.—I am, etc.,

Edinburgh. ARNOLD PINES.

REFERENCES

1 Falk, A., and Stead, W. W., *Transactions of the 15th Conference on the Chemotherapy of Tuberculosis*, p. 127, 1956. Veterans Administration, U.S.A.
2 Emerson, P. A., *Lancet*, 1957, **2**, 674.
3 Pines, A., *Brit. med. J.*, 1957, **2**, 863.
4 Forgacs, P., *Thorax*, 1957, **12**, 344.
5 Emerson, P. A., *Brit. J. Tuberc.*, 1954, **48**, 261.

Medical War Crimes

SIR,—I was much distressed to see in a newspaper article (*Daily Express*, March 4) that Herta Oberheuser, the notorious practitioner of Ravensbruck, has been permitted to resume medical practice in Germany, and this disturbing announcement is merely one example of a highly unsatisfactory state of affairs.

During the War Crimes Trials at Nuremberg, records were produced of experiments conducted on numerous victims in Nazi concentration camps.[1] Most of these unfortunates suffered severely, and many died. In 1951 the Federal German Government, although denying any legal obligation, declared its readiness to grant assistance in special cases of need to the survivors of these inhuman experiments. Now, more than 12 years after the liberation of Europe, the latest German report[2] gives 1,537 claims submitted, 427 grants, and 403 rejected, thus leaving 707 still outstanding. Many of the victims were foreigners, and doubtless some claims have not been submitted. It is not easy for a refugee to obtain evidence of what happened in a concentration camp perhaps 15 years ago.

None of the claimants appears to have received a pension, and the average compensation of only 5,860 DM. (£500) hardly seems proportionate to the injuries inflicted. Neither Ecosoc, the Human Rights Division, nor W.H.O. appears to have investigated the claim by the International Refugee Organization that most of these victims have suffered permanent injury to health, in which case the compensation is obviously wholly inadequate.

I suggest that the British Medical Association should exert its influence to ensure a change of attitude in the medical authorities of Federal Germany, so that the Oberheusers and their victims may alike receive justice.—I am, etc.,

Newcastle upon Tyne. M. H. ARMSTRONG DAVISON.

REFERENCES

1 See Mellanby, K., *Brit. med. J.*, 1947, **1**, 148.
2 See *Plight of Survivors of Nazi Concentration Camps (Fifth Progress Report by the Secretary-General)*, United Nations Economic and Social Council, February 12, 1958.

Gastro-enteritis at Port Said

SIR,—May I use space in your columns to amplify some of the figures given by Major D. J. Cowan, regarding the incidence of appendicitis and gastro-enteritis in Port Said in 1956 (*Journal*, February 22, p. 438)? During the expedition I was the regimental medical officer to some 1,500 troops, all living in the town, but of whom the bulk spent their working day of 12 hours on boats in the harbour. Their diet was tinned "compo," but fresh bread was available. All drinking-water was chlorinated with W.D. water sterilizing powder. Cookhouses were in the open. Sanitation was by bucket in a fly-proof box.

Between November 15 and December 11, 1956, I saw 208 cases of gastro-enteritis which Major Cowan would place in his group 2. The onset of the disease was characteristic: a period of malaise and anorexia followed in two to three hours by severe colicky central abdominal pains, which in about half the cases was preceded by one to five episodes of vomiting. There then followed in 4–6 hours a watery diarrhoea not usually accompanied by either blood or mucus, but these were present on occasions. I usually saw patients first just before or just after the onset of the diarrhoea. At this time they were pale, had temperatures varying from 98.4° F. to 101° F. (36.9–38.3° C.), but about 99.6° F. (37.55° C.) was usual. There was no dehydration apparent. Abdominal examination showed vague tenderness over the whole abdomen, which was frequently most severe centrally or in the right iliac fossa. Guarding and rigidity were very uncommon signs and led to a suspicion of the diagnosis. Examination of the cardiovascular and respiratory systems was normal. The liver and spleen were never palpable and lymph nodes were not palpated in the absence of local sepsis, which was not uncommon. To the best of memory, headache was never so severe as to be a presenting symptom, and I never elicited neck rigidity or Kernig's sign.

The course of the disease followed three patterns: (*a*) 60% completely regressed in 48 hours and were symptom-free without ever being grossly upset. (*b*) 35% showed complete regression of all symptoms in 48 hours apart from the diarrhoea, which persisted for a further three to four days, then abruptly ending. (*c*) 5% showed increasing severity of all symptoms, with severe abdominal colic, extremely frequent stools with urgency of defaecation, dehydration, and temperatures of 101° F. and 102° F. (38.3° and 38.9° C.) in very poorly patients some six hours after they were first seen. This type corresponds most closely with Major Cowan's group 2. At first consultation it was quite impossible to predict which pattern would evolve.

The incubation period was hard to establish; the first batch of patients were seen in a period of 24 to 36 hours after a burst sewage main had flooded their squadron cookhouse area, but two typical cases were seen eight days after the regiment had left Port Said, when the hygienic standards of food-handling, cooking, and sanitation were high. These two isolated cases occurred in soldiers who had been symptom-free in Port Said.

Treatment was symptomatic. At first, cases were given 4 g. of sulphaguanidine 6-hourly, but I felt the drug had little effect, and after December 1 I did not use it and noticed no change in the pattern of the disease. This, however, is in disagreement with the findings of Gosling, Main, and Paros.[1] Reinfections or recurrences were seen in five patients at intervals of up to 17 days. All had been symptom-free from the previous attack for at least four days. The second attack followed the same pattern as the first in each patient and all were of type (*a*).

Of the 208 cases, 30 were admitted to medical units. On November 15, 16, and 17 all cases seen (11) were admitted, but subsequent to this it became apparent that the disease could not be isolated, and the remaining (19) patients were of the (*c*) pattern or two or three of the (*b*) pattern whose diarrhoea still persisted after a week. The differential diagnosis was mainly concerned with noting any change in the natural history of symptoms and signs which might lead to a diagnosis of bacillary dysentery, the enteric fevers, or cholera. All patients were therefore seen at least four times in the first 72 hours of the disease. Cases of sand-fly fever were periodically found, but these always presented with high pyrexia and greater malaise and headache. They were easily differentiated clinically. Appendicitis was always in mind when any of these patients were seen. In all, three cases of appendicitis were seen. Two were diagnosed easily on the basis of vomiting in the absence of diarrhoea, a more constant rather than colicky abdominal pain, tenderness, guarding and rigidity localized in the right iliac fossa, and right-sided tenderness on rectal examination, which was not present in about 20 patients with gastro-enteritis who were examined this way. Two cases were equivocal and sent to hospital for observation. One of these had appendicitis and the second I lost sight of seven days after admission, at which time it was felt he probably had gastro-enteritis. Oral fetor was not found to be a useful sign, nor was withdrawal tenderness in these early cases. In this respect it is of interest to note that in the same regiment only two cases of appendicitis developed between August 11, 1956, and January 26, 1957.

I agree with Major Cowan in the increased incidence of appendicitis during the epidemic, but his figures for gastro-enteritis are mainly of my (*c*) group, as he has noted only the hospital cases, whereas I have endeavoured to show the bulk of cases were treated in the unit. Thus in this statistically insignificant population of 1,500 there were three cases of appendicitis in an epidemic causing 208 cases of gastro-enteritis of unknown aetiology. I had no cases corresponding to Major Cowan's group 1 or group 3.

In regard to aetiology, although no organism could be isolated owing to lack of laboratory facilities, I am convinced that transmission was by way of sewage-contaminated food. For, although our own sewage- and refuse-handling had improved during the four weeks of our stay, the whole living area was soaked by sewage from broken and blocked mains. Once troops could be persuaded to wash their hands before eating and the cooks made to realize the importance of proper fly-proofing and hygienic handling of food, the number of cases dropped dramatically—almost to the extent that the state of a cookhouse could be predicted by the number of its users attending a given sick parade.—I am, etc.,

Catterick, Yorks. M. JOHN OLDROYD.

REFERENCE

[1] Gosling, R. E. G., Main, P. T., and Paros, N. L., *Practitioner*, 1957, 179, 191.

Serial Cholecystography

SIR,—I crave your indulgence and ask to be allowed to reply to Dr. C. Bellamy (*Journal*, March 29, p. 769) and to Dr. Anthony A. Vickers (*Journal*, April 12, p. 888).

After the experimental stage had been completed it was found that little information of value was obtained from the 40, 50, 60, and 70 minute exposures. Therefore in order to reduce the amount of radiation to which the patient was exposed these exposures are now omitted. (The original paper was written more than a year ago.) While it is true that, of the four examples chosen, three were within the child-bearing age, the majority of patients suffering from biliary tract disorders are over 50 years of age. Of 300 consecutive patients investigated and treated in my clinic, 267 were over 40 and 194 were over the age of 50.

The classical cholecystogram gives a positive diagnosis in less than 50% of patients suffering from a biliary tract disorder. There is, as yet, no alternative non-operative method of making an accurate diagnosis (except transparietohepatic vesicular puncture, which exposes the patient to even more radiation) in more than 50% of patients. While agreeing with Dr. Vickers that many elaborate methods of radiology have been devised which have yielded only a little extra information, this stricture cannot be applied to serial cholecystography. The information gained by this method is essential to make a complete and accurate diagnosis of biliary tract disorder.

Until some other non-radiological method of diagnosing biliary tract disorders, and in particular biliary dyskinesia, is discovered, serial cholecystography remains the only available method of supporting a diagnosis and of selecting patients for operation who are suffering from biliary tract disorders. I maintain it is absolutely ethical to expose a patient to such radiation as this method entails in order to raise the proportion of positive diagnoses from under 50% to approaching 100%. As a surgeon I would deprecate abandoning serial cholecystography and resorting to surgical intervention on the clinical findings alone.

I am not competent to reply to Dr. Bellamy's dosage estimation and will leave this to my radiological and physicist colleagues.—I am, etc.,

Newcastle upon Tyne. J. DUDFIELD ROSE.

SIR,—As the radiologists to the Newcastle General Hospital where Mr. J. Dudfield Rose has been carrying out his work on gall-bladder function (*Journal*, February 15, p. 360), may we be permitted to make some observations on the radiation dosages involved?

When this form of cholecystography was first contemplated we were anxious about the number of exposures, and obtained figures of the radiation received by the patient. Since then Dr. Frank T. Farmer (physicist to Newcastle Regional Hospital Board) has measured the radiation received, using a water phantom corresponding to the size of an average patient, with a small ionization chamber.

These results may be summarized as follows:

A.P. View.—75 kV; 60 mas. (milliampère seconds); 40 in. (102 cm.) focal-film distance; 1.5 mm. aluminium filter. Maximum dose to skin for 9 exposures—6.7 r.

Lateral View.—85 kV; 120 mas.; 40 in. (102 cm.) focal-film distance; 1.5 mm. aluminium filter. Maximum dose to skin for 8 exposures—23 r.

Maximum total dose from all exposures to centre of body——1.75 r.

We are fully aware of the necessity of reducing to a minimum the amount of radiation received by patients during any radiodiagnostic procedures, and appreciate the concern which has been shown in the correspondence following Mr. Rose's article. We feel, however, that in any diagnostic investigation the possible risks to the patient must be balanced against the value of the information received leading to the successful treatment of his condition. It is also worth remembering that present dose levels are very much less than those which were being regularly used in some radiological investigations a few years ago.—We are, etc.,

S. M. CAMERON.
T. R. HARLAN.
Newcastle upon Tyne. S. JOSEPHS.

Hypnosis in Surgery

SIR,—Referring to the article by Dr. D. Kelsey and Mr. J. N. Barron on maintenance of posture by hypnotic suggestion, which also describes a plastic operation under hypnosis (*Journal*, March 29, p. 756), it might be of interest to some to know that the late Mr. C. W. Cathcart, F.R.C.S., performed a radical operation for inguinal hernia under hypnosis in the Royal Infirmary, Edinburgh, in 1912.

The operation was successful; no local analgesics were required. At first the surgeon spoke in whispers when he required to speak lest he should "waken" the patient, but he need have had no such fears. At one time he thought the respirations were somewhat shallow, but when the "anaesthetist" told the patient to take deep breaths he did so definitely. At the conclusion of the operation the "anaesthetist" clapped his hands and asked the patient to wake up, which he did as if he was wakening from a natural sleep.

Soon after the patient had been admitted to hospital his own doctor arrived and informed the house-surgeon that the patient was easily hypnotized, and gave the house-surgeon one or two demonstrations. The house-surgeon then hypnotized the patient himself although he had never hypnotized anyone previously. While under hypnosis he suggested to the patient that a blister would rise on his (the patient's) forehead, and it did. It was the house-surgeon who acted as the "anaesthetist" at the hernia operation. As an operation under hypnosis was something of a novelty there was naturally a large gallery of us students.—I am, etc.,

Kirkcaldy. D. G. WISHART.

Acetazolamide and Purpura

SIR,—I think it worth recording a fatal case of thrombocytopenic purpura which occurred in my practice during the administration of "diamox" (acetazolamide). The administration of other sulphonamide derivatives has shown occasional cases of thrombocytopenic purpura, and the makers of diamox—Lederle Laboratories—record in their literature a possible case following the taking of this drug in unnecessarily high dosage.[1]

In my case an unusually active woman, 69 years of age, consulted me with early signs of congestive cardiac failure. The oedema of the legs was controlled by giving one 250-mg. tablet daily, and I found it necessary to give this dose every day. This treatment continued for nine weeks, when the patient developed a generalized purpura, combined with haemorrhages into the muscles of the thighs and blood blisters upon the tongue and buccal mucous membrane. Investigation of the blood by Dr. H. Voss revealed complete thrombocytopenia, bleeding time not less than 15 minutes, a moderate anaemia (haemoglobin 79%), and a low white cell count (75% lymphocytes). She was admitted to

hospital, but quickly deteriorated and died seven days after first consulting me for the purpura.

This must be a rare complication—if indeed the diamox was involved at all. But this drug is being increasingly used in larger dosage than in the case I have described, and over extended periods in such conditions as epilepsy, glaucoma, toxaemia of pregnancy, and congestive cardiac failure. It would be interesting to hear whether there have been any other possible cases as yet unrecorded.—I am, etc.,

Northants. JOHN T. CORBETT.

REFERENCE

1 Reisner, E. H., and Morgan, M. C., *J. Amer. med. Ass.*, 1956, **160**, 206.

Azacyclonol in Schizophrenia

SIR,—Dr. W. B. Wright's letter (*Journal*, April 12, p. 891) implies that azacyclonol is a valuable drug. With this we would not disagree; but for what? Our "firm conclusion" was that azacyclonol is "unlikely to be a very useful drug in the treatment of chronic schizophrenia," and we have yet to see any published data that contradicts this opinion. We stated that we thought azacyclonol had a place in the treatment of hallucinatory states of recent onset, whether schizophrenic or toxic, and most reports on the drug are in agreement on this point. One of us (S. G.) has recently had some success using azacyclonol in combination with E.C.T. in some depressive states, which is of interest, as we formed the opinion, during the trial, that azacyclonol has a "stimulant action," in the sense that it produces increased motor and verbal activity.

Dr. Wright remarks that we did not, in our study, resolve the difficulties inherent in the trial of any drug in chronic schizophrenia. We think that is a fair comment, but would ask who has in fact resolved these difficulties. If the aim of the study is to measure changes in behaviour, it is usually preferable to use a behaviour rating scale dependent on nursing observation. We were primarily interested in changes in hallucinatory experience, and decided that data from psychiatric interviews would be more informative. The dosage was small (60 mg. per day), but the dose of the new psychiatric drugs does tend to rise, and when we planned the trial (April, 1957) this dosage seemed reasonable. As for placebo plus psychotherapy Dr. Wright's suggestion is certainly of interest. One of us (A. D. F.) has recently been involved in a trial of two of the newer phenothiazine derivatives, and included in this trial was a control group who received placebo and twice-weekly interviews. This group in part showed more improvement than did the others receiving the trial drugs (this work is not yet published).—We are, etc.,

S. GRAY.

Edinburgh. A. D. FORREST.

Intra-arterial Thiopentone

SIR,—We are interested in the sequelae of inadvertent intra-arterial injection of thiopentone. Gangrene has been reported after the use of 10% and, in a few cases, of 5% solutions, but we can find no such complication reported after the 2.5% solution now in common use. We would be grateful if any of your readers could supply us with information, which will naturally be treated confidentially, of intra-arterial injection, or of cases where venous thrombosis occurred, when either 2.5% or 5% solution has been used.—I am, etc.,

Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford. D. L. PRYER.

Full-term Extrauterine Pregnancy

SIR,—Cases of full-term extrauterine pregnancy with a living child are now too well known to be reported on specially, but I have often wondered what happened to the patient in later life. The following case, therefore, is of interest.

A Muganda girl, gravida 2, aged about 18, was admitted to Mulago Hospital Maternity Department, Kampala, on August 16, 1955, as a case of acute hydramnios. She had been sent from a small up-country hospital some 22 miles (35 km.) away. As she appeared about full-term and was very uncomfortable, an unsuccessful attempt was made to rupture the membranes. The cervix was long and thin and the presenting part could not be felt. A possible diagnosis of extrauterine pregnancy was therefore made and laparotomy decided upon. On opening the abdomen this proved correct and a living male infant was extracted from the sac. The placenta was found to be very adherent to the bowel, the fundus of the uterus, and the left tubal area. Following the usual practice, no attempt was made to remove it; the cord was ligated and cut short, the placenta left *in situ*, and the abdomen closed. The mother made a good recovery except for a low-grade fever, which had still not subsided in six weeks' time when she insisted on going home. By then the placental mass could easily be felt as a discrete swelling and was still rather tender.

On December 8, 1957, she was admitted again and delivered normally of a full-term female infant weighing 5½ lb. (2.5 kg.) after a labour lasting about eight hours. At first we did not recognize her, as she had lost her papers, but she explained how interested we had been in her before and therefore had come back again for delivery, although it was too far for antenatal care. The previous child, now aged 2½ years, was thriving.

In these cases, at operation, everything appears so stuck together one would imagine that the full-term extrauterine pregnancy with the placenta left inside would be the last. It seems most interesting, therefore, to know that a patient can conceive again so easily. I do not remember having heard of a similar case before.—I am, etc.,

Uganda. CORALIE RENDLE SHORT.

Delivery of the Placenta

SIR,—Many years ago I was faced by the problem of a "delayed" placenta. I kept reminding myself of Chisholm's words, "Masterly inactivity, and watch the fundus."

However, in due course the gamp offered to snuff her. I had not a clue what this meant, and I was too young to admit my ignorance—so I agreed. The gamp thereupon lifted her skirt, her red flannel petticoat, and her bloomers and produced from the top of her cashmere stocking a little metal box. From this she took some brown powder and said to the patient, "Me darlin', snuff this." The woman did so, and there followed three violent sneezes, and behold the placenta was delivered intact.—I am, etc.,

Boston, Lincs. G. R. USMAR.

SIR,—I meant to write a line in the correspondence about expressing the placenta (see *Journal*, April 26, p. 1003). I have watched others practise the barbarous Credé method, and the new methods suggested are really unnecessary today. We need not hesitate, as we used to do, to insert one or two fingers into the vagina and hook the forefinger into the substance of the placenta, which will be found in more than nine cases out of ten doubled up and stuck in the cervix. The left hand on the abdomen brings down the uterus within easy reach.—I am, etc.,

Chigwell, Essex. N. BEATTIE.

Epistaxis

SIR,—I note that the correspondence on the arrest of epistaxis continues, but to date not even your consultant contributor has made the obvious point of principle in dealing with this occurrence. I would suggest that the first-aid principle here is the same as in the arrest of any other form of bleeding—i.e., wherever possible to apply pressure to the bleeding point. Most epistaxis is from the anterior third of the nasal septum, and by pinching the nose it is perfectly easy to apply pressure to the bleeding point and control the bleeding, either till it stops or till medical aid can be obtained. Since these cases may be associated, one presumes, with prolonged bleeding time or clotting time and with hypertension, it is necessary to maintain the pressure for longer than the time that would normally be required to arrest a small bleeding point, and I therefore advise the patient to continue pressure for 15 minutes by the clock; the latter point is most important,

because most patients soon tire of pinching their noses after a few minutes, and 15 minutes appears a long time unless checked by the clock. By giving these rather obvious instructions over the telephone I find the majority of epistaxes are arrested before I arrive at the house, while patients who are subject to recurrent attacks find themselves saved a great deal of inconvenience by adopting this simple measure. I am surprised that it does not appear in the official first-aid manuals.—I am, etc.,

Morpeth, Northumberland. R. P. ROBERTSON.

Vitamin Therapy in Dementia

SIR,—The use of vitamin B in the treatment of toxic confusional states has authoritative support, but its scope is sufficiently ill-defined to make it worth recording a case of dementia from which deductions of value could be more than usually precise.

In November, 1956, I was called to a man aged 71 by his wife. I knew the patient, for I had attended him since February, 1954, for osteoarthritis of a knee and the cervical spine, where marked disk degeneration was noted. Pain was referred down both arms and to the epigastrium. A barium meal demonstrated no abnormality of the upper alimentary tract. In May, 1955, I treated a varicose ulcer, which healed after "elastoplast" support. The patient had worked as secretary to his father's company, and, having ample means, had retired 40 years ago. An operation for piles in 1923 had been his only previous illness. He had not resided abroad. He drank and smoked very little, and he was on the mixed normal diet shared by his family.

When called I found him in bed and needing continuous attention owing to his confusion. He could not find words to complete simple sentences; he could not read, nor could he find his way to his own lavatory. His speech was slurred. His family stated that confusion had been progressive for some months, but that only two weeks before my call he had still insisted on driving his car, to their great concern.

On examination, his reflexes were sluggish but normal. His blood pressure was 170/110. (After three days' rest it was 160/100.) His urine was normal, and his W.R. and Kahn were negative. The only medicaments given were tablets of "becosym-forte" and of nicotinic acid *B.P.* (50 mg.), both three times a day. He improved steadily, and in a month had wholly recovered. He could then drive to the town for shopping, attend to his correspondence and accounts, and had resumed his hobby of gardening. I saw him early in February, 1957, owing to a bruise that appeared for no obvious cause on the left arm. He felt so well that, without seeking advice, he discontinued the tablets at the end of February.

On April 5 I was called to him again owing to a return of the confusion. I found the same failure with words and forgetfulness of familiar facts as heretofore, such as the proper order of putting on clothes, but in a less marked degree. Within a week of return to the same dose of becosym-forte and nicotinic acid he had regained his normal powers. To complete the record I asked Dr. Lazarus Barlow, pathologist at the Royal East Sussex Hospital, Hastings, to examine the blood. He found: Haemoglobin, 11.7 g. (79%); R.B.C., 4,500,000 per c.mm.; colour index, 0.9; W.B.C., 5,000 per c.mm. (polymorphs 70%, lymphocytes 27%, monocytes 3%). Blood film showed slight anisocytosis and anisochromia of the red cells. The leucocytes and platelets appeared normal. E.S.R. (Wintrobe) was 29 mm. in one hour (normal 0-9 mm.). The patient remains well and drove his car through Norway on holiday last summer.

Perhaps from this can be deduced that some cases of senile dementia will respond dramatically to concentrated vitamin-B therapy.—I am, etc.,

Battle, Sussex. W. E. DAVIDSON.

Care of the Epileptic

SIR,—I am afraid that Professor A. Mair's letter on "Care of the Epileptic" in your issue of April 12 (p. 889) is a little misleading in its references to the Post Office. The proposal that was put to the Post Office by the Scottish Epilepsy Association was that this postal sorting work should be provided on a contract basis to be performed by epileptics in their own employment unit. You will appreciate that superannuation considerations would not have been relevant in these circumstances. They were not in fact given as a reason for our inability to accept the suggestion, which was based on technical consideration. I am glad to say, however, that last October we were able to give the association a contract for other work—namely, the repair of switchboard cords.—I am, etc.,

T. A. O'BRIEN,
Public Relations Officer,
General Post Office.

London, E.C.

British Qualifications Abroad

SIR,—Should the L.M.S.S.A. and the M.R.C.S., L.R.C.P. be scrapped? These qualifications need serious review in the light of their value outside Britain. In the United States, 19 of those States that accept foreign doctors do not recognize them. This limitation extends to working in a hospital under supervision, so that even those Conjoint men who would like a short experience of American medicine may be barred in many places. Canada has adopted at least as much from American medical structure as from the British; and we cannot predict what changes will take place in this Dominion during the next few years. In both the United States and Canada the qualifying examination is called the "M.D." There is only one standard of qualification, whereas in Britain there are three—L.M.S.S.A.; M.R.C.S., L.R.C.P.; and the M.B. I do not think the United States or Canadian M.D. is more difficult than the Conjoint, but is there still a justification for this triple standard in Britain? In the past so many got their second M.B., and then balked at the Finals. Lured by the prospect of earning money soon, or because they had squandered their patrimony on riotous living, or because they had married, they took the Final Conjoint and were content. In a Welfare State these reasons lack force. Regarding those two great monoliths, the F.R.C.S. and the M.R.C.P., I do not think there is anything quite so rugged on this side of the Atlantic.—I am, etc.,

Hamilton, Ontario. I. M. GRIFFITH.

Rheumatology as a Whole-time Specialty

SIR,—Dr. Marjorie Dobson in her letter (*Journal*, March 29, p. 776) demands that rheumatology be recognized as a full-time specialty, and the rheumatologist as a specialist both by the State and by those who practise medicine within or outside its service.

No practising doctor will dispute the fact that rheumatology is part of general medicine, but in my experience the stumbling-block is in the day-to-day practice of medicine in which the State and the public rightly have a big interest. The general physician has neither the time nor usually the knowledge for the complete and successful management of the patient who is suffering from "rheumatism," a term which includes a variety of disorders. The physician specializing in cardiology or neurology, who is rightly recognized by his colleagues in the medical profession as a specialist, confines his activities in the main to diagnosis, as is obvious to those doctors who practise what is termed physical medicine and find themselves responsible for much of the management of these cardiological and neurological patients. That there is also a place for the physician who has particular experience in the diagnosis of rheumatism and the management of rheumatic patients is shown by the frequency with which the general practitioner sends his patients to such a physician for advice. Whether or not he should be the director of the department of physical medicine to which the general practitioner refers his rheumatic patients for treatment is debatable. But we should perhaps wait a little, think, and plan before backing Dr. Dobson's demand for a new whole-time specialty of rheumatology.—I am, etc.,

London, W.1. FRANCIS BACH.

SIR,—One wonders whether Dr. M. M. Dobson (*Journal*, March 29, p. 776) realizes that there already exists a specialty that embraces the scope of the work which she

says merits the establishment of rheumatology as a separate entity. This is physical medicine, which is already well established and recognized by the majority as providing the ideal specialty to deal with the treatment of those "rheumatic disorders" which lie neither within the province of the general practitioner, the general physician, or the orthopaedic surgeon. There would therefore seem to be little point in encouraging the growth of rheumatology beyond the few established specialized centres.—We are, etc.,

MICHAEL E. FEARNLEY.
P. HUME KENDALL.

Orpington, Kent.

Intestinal Atresia

SIR,—It has been suggested[1,2] that ischaemia of the small intestine in the foetus may result in atresia. For the last two years I have been investigating the relationship of blood supply to growth of the foetal gut with particular reference to the aetiology of post-duodenal gut atresia. While such a study is possible in foetuses having a normal gut, the investigation of the blood supply of the small intestine in foetuses with atretic bowel is extremely difficult because of the scarcity of such material. I therefore wish to have the opportunity of examining any foetus or stillborn infant showing small-bowel atresia at necropsy in order that I may inject such specimens and remove tissues for histological examination. I would be most grateful to be informed of any such specimen: the unfixed foetuses should preferably be deep-frozen until arrangements can be made for collection of material.—I am, etc.,

E. PATRICIA LEES.

Department of Anatomy,
University of Liverpool,
Liverpool, 3. (Phone: Royal 6022, Ext. 27.)

REFERENCES

[1] Louw, J. H., *S. Afr. J. clin. Sci.*, 1952, 3, 109.
[2] Barnard, C. N., *Surg. Forum*, 1957, 7, 393.

POINTS FROM LETTERS

Gastro-duodenal Ulcer

Dr. J.-JACQUES SPIRA (London, W.1) writes: In his review of my monograph on gastro-duodenal ulcer (*Journal*, April 5, p. 817), Dr. F. Avery Jones expresses the view that "any book in this field must bear concrete comparison with the monumental volume produced by Ivy, Grossman, and Bachrach." I wonder why? Having read their book from cover to cover I could not find the "keen critical commentary" referred to by your reviewer nor a single original contribution towards the solution of the peptic ulcer problem. Its only value appears to me to be the exhaustive compilation of statistical data. If your reviewer had only read the introductory quotations from Bertrand Russell and S. J. Thannhauser he would have perceived the purpose of my book and the obvious reasons for omitting statistics of the results of my treatment. . . . I am sorry that Dr. Avery Jones did not find a "single factual statement" in my book; he could not have read the captions of the radiographs which illustrate a few typical results of my treatment. In publishing my monograph the intention was not to attempt a comparison with the American book but to contribute new ideas and throw fresh light on a most serious but perhaps not quite so baffling a medical puzzle.

Disease Education by the B.B.C.

Dr. D. W. SIMPSON (Bawtry, Yorks) writes: I agree wholeheartedly with Dr. A. Cameron's letter (*Journal*, April 12, p. 893), but surely a letter of this description would be better placed in the daily press than in the *B.M.J.* The vast majority of general practitioners are by now all too aware of the neuroticogenic effects of these B.B.C. programmes, and it is the general public, not the doctors, who should hear of these tragedies.

Aphthous Ulcers

Dr. G. E. KING-TURNER (London, S.W.16) writes: I have read with great interest Dr. E. M. Donaldson's letter (*Journal*, April 26, p. 1004) on aphthous ulcers. Drs. S. C. Truelove and R. M. Morris-Owen (*Journal*, March 15, p. 603) seem to have evolved a highly complicated treatment. . . . After thirty years of dental practice I have treated a very large number of these cases successfully. The treatment consists of the administration of dilute hydrochloric acid in the usual way after meals.

Obituary

J. C. MACKWOOD, *M.C.*, M.R.C.S., L.R.C.P.

Dr. J. C. Mackwood, who was in general practice in the south of England before he became a psychotherapist, died peacefully at sea on April 5. He was 72 years of age.

John Charsley Mackwood was born at Colombo, Ceylon, on August 3, 1885. From Charterhouse School he entered the London Hospital Medical College, and qualified M.R.C.S., L.R.C.P. in 1910. After holding the appointments of assistant house-surgeon and house-physician at the Poplar Hospital and house-physician at Tunbridge Wells General Hospital, he settled in a country practice at Newick, near Lewes, in Sussex. There he held several public appointments and was medical officer to the Lewes workhouse at East Chiltington. During the first world war he served as a temporary captain in the R.A.M.C., and was awarded the Military Cross in 1917 because, in the words of the official citation, "He attended to the wounded of eleven units in the open under heavy shell-fire, working singlehanded for several days. His self-sacrificing devotion to duty and his thoughtfulness and care of the wounded were beyond praise." After the war he returned to his practice at Newick, and, in addition, became medical referee to the East Sussex war pensions committee and to the Lewes area of the Ministry of Pensions. In 1925 he left Newick for Brighton, but stayed only two years or so before moving on to Parkstone, in Dorset, where he was in partnership with Dr. J. L. Graham-Jones for some years. After a brief spell at Horsham, Sussex (1933–6), he moved to London and became clinical assistant at the Tavistock Clinic. A little later he was appointed psychotherapist to the psychiatry department of the West End Hospital for Nervous Diseases (now the West End Hospital for Neurology and Neurosurgery) and clinical assistant in the psychiatric department at St. Bartholomew's Hospital. From 1943 until he retired in 1952 he was a psychotherapist at Wormwood Scrubs prison. He leaves a widow.

H. K. S. writes: In February, 1943, Dr. J. C. Mackwood was appointed to undertake the treatment of certain mentally abnormal prisoners selected as suitable subjects for psychological treatment. He joined the staff of Wormwood Scrubs on a part-time basis when the psychotherapy unit at that prison was reopened in 1943 under the general direction of Dr. H. T. P. Young, the then senior medical officer. Dr. Mackwood was always a most thorough and painstaking man, and his notes and reports on his cases were both exhaustive and informative. A few years later the establishment of a special ward for prisoners undergoing psychotherapy led to the development of group therapy; he was a pioneer in this form of treatment, and his therapeutic groups at Wormwood Scrubs were the first to be held in any prison in this country. He published several papers, and I would mention in particular "The Psychological Treatment of Offenders in Prison" (*British Journal of Psychology*, 1949); his chapter on remedial and educational psychotherapy during penal detention in *The Roots of Crime* (Butterworth, 1954); and his report of his work at Wormwood Scrubs in the Prison Commissioners' Annual Report for 1949. A quiet, unassuming man, he was always a helpful and congenial colleague and ever ready to discuss his cases. He had a tolerant appreciation of the problems and difficulties in the way of this form of treatment under prison conditions, while advocating a greater elasticity. He was a man of high ethical principles and exhibited an earnest sincerity in his medical practice. It was a privilege to be associated with him in his prison work.

E. B. S. writes: Those who knew John Mackwood intimately—and he was a good and loyal friend—will be aware that his great success in the field of psychotherapy was due more to his personal qualities than to any rigid

method which he might have employed. In point of fact, he had the art of adjusting his method to the needs of each particular patient. In addition to his public appointments, John Mackwood ran a deservedly flourishing private practice. He was a happily married man who will be mourned not only by his widow but by his select circle of friends as well.

GERALD ROBINSON, F.R.C.S.

Mr. Gerald Robinson, consulting surgeon to the South Devon and East Cornwall Hospital, died on March 20. He was 76 years of age.

Gerald Charles Frederick Robinson was born in London in 1882, the son of an artist, and was educated at Marlborough School and Guy's Hospital, where he was awarded the treasurer's gold medal for clinical surgery in 1903. Qualifying M.R.C.S., L.R.C.P. in 1904, he was admitted F.R.C.S. in 1907. After qualification he held the appointments of out-patients' officer and house-surgeon at Guy's Hospital and clinical assistant at the Evelina Hospital for Sick Children. He settled at Plymouth in 1907 in partnership with the late Dr. Hughes, and shortly afterwards became honorary anaesthetist to the South Devon and East Cornwall Hospital. In 1911 he was appointed assistant surgeon to the hospital, becoming full surgeon in 1919, and ultimately senior surgeon. He retired from the hospital staff shortly before the introduction of the National Health Service in 1948. During the first world war he served as a captain in the R.A.M.C., and for a time was surgeon to a hospital for officers at Plymouth. He was also consulting surgeon to the East Cornwall Hospital, Bodmin, and to the Liskeard, Fowey, Kingsbridge, and Totnes hospitals. For some years he was honorary librarian to the Plymouth Medical Society, of which he was president for a term. Mr. Robinson had many interests outside his profession. An expert metal-worker, he was a member of the Guild of Silversmiths, and was always ready to help friends by making spare parts in brass or copper in his own workshop. He was also a skilful fisherman, a good shot with both shotgun and rifle—he competed at the National Rifle Association meetings at Bisley—a keen ornithologist and wildfowler, and, in years gone by, a yachtsman. Mr. Robinson was a widower, his wife having died in 1955.

We are indebted to Mr. G. L. Preston, F.R.C.S., for the following appreciation (originally printed in the *Western Morning News*): The passing of Mr. Gerald Robinson brought an acute sense of loss not only to his many personal friends but to the medical profession generally and to all who knew him. Modest and retiring, and rather reserved almost to the point of extreme shyness at times, he always avoided publicity, a trait that endeared him even more to those friends who knew him intimately, but one that was often misunderstood by those who did not know him so well. There is an old saying, "A successful man is known during his lifetime, but a great man is known only after his death." To be a great man and a successful man during a lifetime is surely the highest tribute that can be paid to one so deserving as Gerald Robinson.

A. de St. L. F. PERIGAL, M.D.

Dr. A. de St. L. F. Perigal, who was in general practice at New Barnet for over 30 years, died on April 3 at Worthing, where he had been living in retirement. He was 83 years of age.

Arthur de St. Leu Frederick Perigal was born at Wheatley, Oxfordshire, on January 12, 1875, the son of Dr. Arthur Perigal, and was educated at Queen Elizabeth's Grammar School, Barnet, Fettes College, and Edinburgh University, where he graduated M.B., Ch.B. in 1898. Four years later he proceeded to the M.D., with commendation. After holding the appointments of junior house-surgeon at the Lincoln County Hospital and house-physician at the Brompton Hospital, he served as civil surgeon at the Western Heights Hospital, Dover, during the South African war. Later he went to the Rotunda Hospital, Dublin, for postgraduate study. In 1906 he married Constance Adeline, the only daughter of Dr. William Fox, of New Barnet, and in the same year entered into partnership with his father, Dr. Arthur Perigal, in New Barnet. On the retirement of his father some 20 years later Dr. A. F. Perigal continued to serve in the district until he himself retired from general practice in 1937. During these 31 years he was an active physician at the Victoria Cottage Hospital, Barnet, and was known and loved by a wide community.

In his earlier days Dr. Perigal was a keen rugby player and a cricketer of skill, and he retained his interest in these games to the last. Shortly after he graduated he was awarded the Royal Humane Society's certificate for life-saving while he was at Southwold. He was a great walker and lover of nature and also a water-colour artist of some distinction, a talent he inherited from his grandfather, who was a Royal Scottish Academician. During his retirement, spent at Hatfield during the years of the second world war, Dr. Perigal assisted his medical colleagues in many ways, though he was becoming increasingly deaf. In 1946 he moved to Worthing with his family and continued his interest in medicine through his connexion with the West Sussex Division of the British Medical Association. He had previously been chairman of the Barnet Division in 1934–5. In his declining years, despite increasing handicap in health, he retained his interest in all around him, his family, friends, young and old, his profession, his school, and the love of art and beauty. He is survived by his widow, daughter, and son.

E. CRONIN LOWE, M.B.E., M.B., B.S.

Dr. E. Cronin Lowe, formerly a clinical pathologist at Southport and at Liverpool, died in a nursing-home in Southport on April 12. He was 77 years of age.

A New Zealander, Edward Cronin Lowe was born at Dunedin on September 20, 1880, the son of an engineer who was responsible for the laying of that country's railways, and as a boy he developed a pioneering instinct and a love of the countryside. He was educated at Wellington College, New Zealand, and, after coming to England in 1899 as a medical student at Guy's Hospital, he graduated M.B., B.S. in 1905.

From 1907 to 1915 he was in general practice at Southport. During the first world war he served as pathologist to the New Zealand Division from 1916 to 1919 with the rank of captain, and was appointed M.B.E. for his work on immunization during the influenza epidemic of 1918. From 1919 to 1948 he was honorary consultant pathologist to the Southport Infirmary, and at about the same time he was on the staff of the Liverpool Eye and Ear Infirmary and the Homoeopathic Hospital. Chairman of the Southport Division of the B.M.A. in 1936–7, he represented his division at one or two Annual Meetings.

He was an indefatigable research worker, always feeling for a deeper and wider understanding of disease and not afraid of being unorthodox. Far into the night he would work in his own laboratory on such problems as the sero-diagnosis and the aetiological factors in cancer. His work on pathogen selection in the preparation of vaccines is well known, and he read a paper on this subject at the First International Congress of the Royal Institute of Public Health at Zurich as early as 1929. As his work on infective foci and their treatment continued, he developed the use of oral vaccines, which he made himself. In the early days of blood transfusion Dr. Cronin Lowe was the first man in the district to type donors and recipients and carry out transfusions in suitable cases.

He married in 1905 Helena Fruen, by whom he had three daughters, one of whom, also a pathologist, is now the wife of Professor R. M. Gordon, of the Liverpool School of Tropical Medicine.

H. R. writes: Dr. Cronin Lowe will be remembered chiefly as a man who enjoyed the fullness of living. His early

experiences as a boy gave him a zest for camping and fell-walking, and no one could wish for a more delightful companion. As a raconteur, especially when sitting around a camp-fire, he kept his audience spellbound. He also knew how to work with his hands. Having discovered a large disused lumber shed on the banks of Lake Windermere, he transformed it, with the help of his daughters, into a boat-house combined with banqueting-hall and living-quarters for his family and his many guests. His home in Southport was the centre of many activities, his wife being a gifted portrait-painter and his daughters having inherited highly artistic faculties, especially drawing and painting, together with a love of nature. He himself made an extensive collection of photographic slides which he coloured by hand. Both he and his wife, being deeply religious, took a very active part in foreign missions and in religious work in Southport. His last long illness was borne with that patience and courage and cheerfulness which characterized his whole life, and inspired everyone who came in contact with his vivid and lovable personality.

HÉLÈNE NORRIS, M.D., L.M.S.S.A.

G. M. S. writes: As one who collaborated with Dr. Hélène Norris from time to time in the treatment of her patients, I would wish to add my tribute to that in the *Journal* of May 3 (p. 1068). Dr. Norris prepared notes about her patients with the most scrupulous care. No detail was left unrecorded. In addition one was impressed by the way in which she had reviewed both the social and the medical aspects of the case. Though small in stature, she impressed her patients greatly, and their confidence in her was unbounded. She was fully aware of the seriousness of the disease from which she had suffered, but her quiet courage was all the more impressive. Her one desire was to live as long as possible for the sake of her husband and the son to whom she was so devoted. She had a dignity that belonged to earlier ages, and one salutes a courageous woman who lived up to the ideals in which she believed.

Medico-Legal

FINGER-PRINTING

[FROM AN EXPERT IN FORENSIC MEDICINE]

The news that Japanese research workers have developed an autoradiographic method of detecting finger-prints on paper or cloth[1] has aroused interest in police departments in this country.

The material left behind in a finger-print is of course sweat containing minute traces of body chemicals. By this new method cloth, paper, etc., suspected of harbouring finger-prints is exposed to a vapour of formaldehyde containing radioactive carbon atoms. The formaldehyde becomes "fixed" on the proteins of the finger-print, and the radioactive carbon is distributed as an exact copy of the finger-print. The treated material, after the removal of any residual formaldehyde, is then clamped to a photographic film and placed in a light-proof box in a refrigerator. Development of the autoradiograph takes from one to eight days. The authors of the method claim that any latent finger-prints, except those on silk or woollen fabrics, can easily be detected in this way so long as the finger-print protein persists. Recently, also, Davis[2] has shown that finger-prints can be obtained by histological section to a depth of 0.6 mm. beneath the surface of the skin, and suggests that this method could be used in the identification of bodies in whom the surface-prints have been deliberately abraded by the murderer.

It was in 1823 that Purkinje[3] first classified finger-prints, and in 1880 Sir William Herschel[4] used finger-prints in his administrative work in India to prevent impersonations. Henry Faulds[5] and Sir Francis Galton[6] separately suggested methods of classification in 1892, and nine years later Sir Edward Henry[7] adopted Galton's classification and set up the finger-print bureau at New Scotland Yard. In 1905 finger-prints were used successfully in a murder case in Britain. Since then the use of finger-prints has become universal, and the chances of any two persons having the same finger-print are said to be one in thirty times the population of the world.

To "lift" a latent finger-print on a smooth surface such as glass, a table, or a blunt instrument like a tyre-lever it is necessary to make it visible for photography by outlining it with a fine powder applied with a soft brush. Various powders have been used, including aluminium, willow charcoal, lamp-black, powdered graphite, and white lead—the last was the cause of a case of chronic lead poisoning described by Nyfeldt.[8] The most widely used powder, however, is made of mercury and chalk (grey powder). Mercury poisoning in police officers has undoubtedly resulted from the use of this powder,[9–11] but simple precautions such as the addition of dextrose to inhibit oxidation of the mercury, the use of overalls, and the washing of hands appear to be sufficient to overcome the risks.

The use of radioactive carbon will certainly raise doubts in minds conditioned by the popular press to the dangers of all forms of radiation, but carbon-14 with a half-life measured in thousands of years is unlikely to be any more dangerous than grey powder, though of course considerably more expensive. It is encouraging to find that modern scientific advances are being applied to well-established methods of criminal investigation.

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ACCIDENTAL DEATH BY HANGING

[FROM A PSYCHIATRIC CORRESPONDENT]

Last December an air crew navigator, 34 years of age, was found dead in a hotel bedroom. He had hanged himself, naked, by knotting the ends of a towel under his chin and hanging the centre of it over the door of a built-in wardrobe 6 ft. 7 in. (200 cm.) high. The subject himself was 6 ft. (183 cm.) tall, and when found his feet were touching the ground. The towel, which was tied in a half-knot, was removed by the police simply by slipping it over the subject's head. The only details available about his previous personality were that he was steady and efficient at his work, that he had seemed to one witness to be aloof, and that he had recently informed a colleague that he had studied hypnotism for many years, had not practised it recently, but was thinking of studying it further. In his room a notebook was found containing numerous notes on hypnotism.

Post-mortem examination showed an irregular pressure mark consisting of a series of folds running across the front of the neck just below the larynx and rather sharply upwards behind both ears. The certified cause of death was asphyxia due to strangulation by hanging. The verdict in the Coroner's Court was "asphyxia due to hanging while engaged in an experiment in autohypnosis. (Accidental.)"

Comment

Cases such as this can provide difficult diagnostic problems, and it is not always possible to say with certainty whether suicide or accident accounted for death. What are the arguments in the case described? Death by hanging

is a common form of suicide, and therefore there is usually a strong presumption in favour of suicide. That the individual's feet were in contact with the ground does not exclude this diagnosis; and the fact that he appears to have been a solitary and introspective individual might be held to support it. In a case of suicide even a major portion of the trunk may be found in contact with the ground.

On the other hand, reduced oxygen supply to the brain is known to assist hypnosis, and the deceased was certainly interested in the subject. And, although there was no unequivocal evidence that he had actually practised autohypnosis, he might have been conducting some sort of experiment. Apart from the contents of his notebook, no other clue was found to suggest the exact nature of the experiment. The fact that he was naked could possibly be read as meaning that the experiment had some sexual component. What may have been initially only slight pressure of the towel round the neck, by producing first a disturbance of judgment and control by obstruction of the cerebral circulation and then loss of consciousness, could perhaps have ended in causing the experiment to miscarry fatally. Where death by strangulation is the accidental result of an experiment, loss of consciousness is more likely to have been due to interference with the cerebral circulation than to obstruction of the air passages, because of the former's more insidious and less unpleasant onset.

Psychopathologically, morbid experiments involving a risk of accidental death have some determinants in common with suicide. We do not know how often such experimentation occurs, since it is carried out alone and in secrecy. Only exceptionally is it fatal.

DOCTORS SENT FOR TRIAL

After a two-day hearing at Tower Bridge Court, Dr. Louis Newton and Dr. Ellis Stungo were committed on May 2 for trial at the Old Bailey. They were charged with offences in connexion with the death of Miss Jean Cook, an Australian nurse (see *Journal*, April 26, p. 1009). Both defendants pleaded not guilty and reserved their defence. A submission by Mr. Christmas Humphreys that there was no case for Dr. Stungo to answer was rejected by the magistrate (*The Times*, May 3).

Medical Notes in Parliament

POLIOMYELITIS VACCINE

The debate on the interruption in the supplies of poliomyelitis vaccine, which the Opposition initiated on May 1, became the platform from which the Ministry of Health announced the decision to suspend, as a temporary measure, the British tests of imported vaccine. The Opposition insisted on recording their dissatisfaction in a division, from which the Government emerged with a majority of 66.

Improvidence Charged

The charge which Dr. EDITH SUMMERSKILL (Warrington, Lab.) brought against the Minister on behalf of the Opposition was, in short, that he had failed to make the necessary provision to safeguard sections of the population against poliomyelitis; and that over recent weeks questions designed to elicit information had been met with persistent evasion and dialectics. The latest figures, for February, showed that of the total then registered 571,000 had been given one injection and 2,688,000 were still waiting for the first injection. Thousands more, it was estimated, had been registered in March and April. The debate, said Dr. Summerskill, was a culmination of a growing demand in Parliament and among the public and the medical profession for the Minister to give top priority to this matter before the summer arrived. She disputed the Minister's statement on April 21 that delays in the delivery of vaccine from the four original sources of supply—two British firms, one Canadian, and one in the United States—were due to different causes "but in no case was it within the control of or due to the fault of the Government." There was a large exportable surplus of Salk vaccine in America, and the fault was that the Minister failed to arrange in time to have it sent here. The Canadian supplier had been reported as saying there was a "misunderstanding in London," as the contract was for supplies before the end of June. The two British drug houses should have had the assistance of the Ministry in technical advice and help to obtain any equipment they wanted. Mr. Somerville Hastings, she recalled, had suggested two weeks before that it might be a good idea for the State to produce this vaccine, but the Minister had treated it as ridiculous. Why should it be?

Mr. D. WALKER-SMITH: Because these two companies have as good scientists, technicians, facilities, and equipment as can be found anywhere.

Dr. SUMMERSKILL said she did not accept the suggestion that private drug houses needed no help or advice. The Minister had said that some batches of vaccine had failed to reach the standard. That was a weak excuse. Everyone with any knowledge of the subject knew that could be expected. Whatever the nature of the scheme the Minister had improvised to cover his neglect, many thousands of those registered would still be waiting for immunization at midsummer.

Minister's Defence

Mr. WALKER-SMITH began his reply by emphasizing the complexity and difficulty of the manufacturing processes involved. It took nearly five years after the basic laboratory discoveries to manufacture enough vaccine for field trials. To read some newspaper comment one would think that making this vaccine was no different from making toothpaste or ice-cream. Going back to last September, and the decision to offer vaccination this year to priority groups, he said the Government could then look to two main sources of supply, British vaccine and Salk vaccine—the British containing the Brunenders type I strain of virus, and the Salk containing the Mahoney strain. The Medical Research Council advised last year that Salk vaccine should be regarded as a temporary supplement to bridge the gap until enough British supplies were available; that such vaccines should be check-tested by the M.R.C.; and that people should be given the right to refuse Salk vaccine if they preferred to wait for the British. With this advice in mind the Government placed orders for 5,000 litres of Salk vaccine, 4,000 from Canada, and 1,000 from the United States. He described the testing processes, and pointed out that all were sample tests; they could not altogether exclude risk and guarantee safety, but they did minimize it to relatively small proportions. Concurrent testing, on different samples from the same batches on both sides of the Atlantic, ensured the maximum potency period for distribution and use of what was a perishable commodity. It implied forward orders, placed for delivery at a future date, subject to satisfactory testing. That imposed a certain inflexibility compared with the purchase of Salk vaccine "off the shelf" and the acceptance of American tests as sufficient.

It had been suggested that not enough was purchased originally. The reasons were the advice from the M.R.C. that the import should be a temporary measure only; there was no reason to foresee at that time the almost total interruption of British supplies that had occurred; and that parents were given the right to refuse Salk vaccine, and so no estimate could be made of the degree to which it would be accepted. Expert advice, then and still, was that British vaccine when available was the best because of the Brunenders instead of the Mahoney strain. There were substantial consignments from British sources into January and February of this year. The difficulties which struck the two British companies involved a wide range of their production potential. He regretted these events, but he did not and would not utter a syllable of reproach. No blame could be or should be attached to the companies,

who were of great and deserved reputation. Immediate steps were taken to remedy the deficiencies, and in January 2,800 litres of Salk vaccine were ordered, with the expectation of emerging from the tests, if successful, in April and May. This would have been the main, but not the only, source of supply for the present period. Difficulties also occurred across the Atlantic. One batch of Canadian Salk was withdrawn because it was not up to standard, and two batches were pre-empted for Canadian use. There was no question of any breach of contract by the Canadian suppliers. The balance of their deliveries was expected by June. Half a million doses arrived on April 29 and were in process of rapid distribution. Of the 2,800 litres of American Salk ordered in January, one part of the first large batch of 1,500 litres showed on test by the manufacturers a minute contamination of live virus. This discovery, microscopic though it was, led to the immediate and unquestioned discarding of the whole batch. It also meant that the American authorities would require negative tests on five successive batches before allowing one further batch to be issued. The immediate consequence was the loss of 1,500 litres expected soon after Easter.

M.R.C.'s Advice

A further consequence was that some large items in the pipeline must be considered at risk. The combined effects of these events presented a double problem—(1) the acquisition of further vaccine; (2) the time factor in its use. On the second it was right that the Government should seek advice from the M.R.C. whether, in view of the shortfall, American and Canadian Salk vaccine which had satisfactorily passed safety tests and been licensed for issue in the country of origin should be made available for issue in this country without first being subjected to the further tests of the M.R.C. The Council had given a reasoned opinion,* and listed its order of safety—first, vaccine made according to the British formula which had passed British safety tests; second, imported vaccine from America and Canada which had passed safety tests in the country of origin and also the British tests; third, imported vaccine from the same sources which had passed safety tests and been licensed for issue in the country of origin. The Government accepted that advice, and would act at once upon it. The Government also accepted the longer-term advice of the M.R.C., and proposed to restore check testing by the Council at the earliest possible moment. They, like the Council, looked forward to the possibility of one day being able to dispense with the need to use any vaccine containing the Mahoney strain, but that day was not yet. Meanwhile people would still have the right of refusal, if they preferred to wait either for British vaccine or for Salk vaccine tested by the M.R.C. It was a decision that the individual might find hard, but he could take his doctor's advice.

In those two speeches lay most of the threads of the subsequent short debate. Mr. SOMERVILLE HASTINGS (Barking, Lab.), for example, upbraided the Minister for failing to realize the type of disease with which he was dealing, the desirability of a third dose, and need for greater home production by using other firms. Mr. R. FORT (Clitheroe, Con.), a lay member of the Medical Research Council, voiced some nervousness about Salk vaccine with the Mahoney strain, but said that, as he had listened to the discussions of his professional colleagues on whether or not it should be used, he could only concur with what they advised. The decision was made on a very nice balance of argument.

Mr. Edelman's Questions

One speech, however, provoked considerable anger and a hot retort from the Minister. Mr. M. EDELMAN (Coventry, North, Lab.) wanted to know of the Minister whether any undertakings, written or verbal, had been given to Burroughs Wellcome and Glaxo that they would have priority in contracts for the vaccine; in other words, were there any considerations, not medical but commercial, that had resulted in giving priorities and preferences to these two firms? He quoted from a letter he had received, he said, from a doctor, making a serious charge against the Ministry—one which he repeated with all responsibility because he felt there were many points, not only of maladministration but of some commercial preference in the allocation of contracts. He could not help feeling, whatever the medical rationalization, that there might have been commercial factors involved in the allocating of contracts, and which deserved the closest scrutiny. The letter from a doctor stated: "I can only believe there is some black agreement between the Ministry and the commercial firms in England not to import American or Canadian vaccine. If this is so, a manslaughter charge should be brought . . . every time a British child dies from acute anterior poliomyelitis." He finished up with a demand for a good shake-up at the Ministry and the resignation of the Minister who had defended its damaging ineptitudes.

Mr. WALKER-SMITH gave a direct answer when he wound up the debate. No undertakings whatsoever had been given to Glaxo and Burroughs Wellcome. The Medical Research Council preferred British vaccine on purely medical grounds. No money whatsoever, apart from the purchase price of the vaccine, had been given to those companies. Then he went on, "In the smears and unfounded allegations which he [Mr. Edelman] made against the Medical Research Council and against these companies he plumbed depths of squalor which I had not previously experienced. Behind the cloak of Parliamentary privilege he has behaved in a disgraceful way to make those allegations, and we shall look forward with interest to see whether he has the courage to repeat them outside, where he will be mulcted in heavy damages if he does." No advisers of the Ministry, Mr. Walker-Smith added, were in any way connected with Burroughs Wellcome or Glaxo, nor was any member of the M.R.C., although the firms might of course ask the Council for advice. The Minister disclosed in this reply that there was at least one other company which was contemplating production of this vaccine, though as it was not as far forward as the other two its potential had not figured in the calculations.

*See p. 1117.

ANSWERS TO QUESTIONS

Russian Vaccine for Multiple Sclerosis

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister of Health on April 28 whether he would consult with the Medical Research Council with a view to obtaining a supply of the Russian vaccine for multiple sclerosis for the purpose of conducting, in this country, suitable tests of the efficacy of this vaccine. Mr. WALKER-SMITH replied that no final decision could be taken on the use of this vaccine until information about it was received from the Soviet Union. In the meantime, in view of the evidence available from laboratory investigations carried out in the United Kingdom and in America, which threw doubt upon both its safety and its effectiveness, the Medical Research Council did not propose to undertake clinical trials of its possible value in the treatment of multiple sclerosis.

Dr. JOHNSON pointed out that the Minister had said he would allow imports of this vaccine through private sources. Could the Medical Research Council give any guidance for the benefit of people who were anxious to effect such imports if the vaccine was any good? Mr. WALKER-SMITH replied that the imports were on the individual guidance and responsibility of a general practitioner recommending them. In the general sense, tests would take a long time to carry out. Meanwhile, pending information from Russia, Dr. Johnson might be interested to look at the conclusions of Professor Dick, published in the *British Medical Journal** earlier this year, and also to study the conclusions of Dr. Sabin, of Cincinnati, when they were published.

*Dick, G. W. A., McKeown, Florence, and Wilson, D. C., *Brit. med. J.*, 1958, **1**, 7.

Mr. HASTINGS asked the Minister on May 5 if, after having received the information from Russia that he was seeking, he would issue a White Paper on the Russian vaccine for multiple sclerosis, so that both doctors and the public might have reliable information available. Mr. WALKER-SMITH said he did not think this course would be appropriate, since the responsibility for using the vaccine must rest with the doctor, not the patient. He would continue to ensure that any information reaching him was made available to doctors who wished to use the vaccine.

Senior Registrar Posts

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked the Minister of Health on April 29 how many specially designated senior registrar posts he intended to approve; what guidance he was giving to regional hospital boards; and what would be the higher rate of pay attaching to these posts. Mr. WALKER-SMITH stated that the number of posts to be approved would be decided on merits after the board's proposals had been received. He was about to discuss with the Joint Committee the guidance to be sent to boards. Rates of pay would be a matter for negotiation.

Hospital Medical Staffing

Mr. ROBINSON asked him on May 5 if he would widen the membership of the proposed working party on the medical staffing structure of the hospitals to include representatives of other bodies than the Joint Consultants Committee and his department. Mr. WALKER-SMITH replied that the Secretary of State for Scotland and he were not proposing any change for their part. Mr. ROBINSON said there were those in the profession who believed the advice the Minister would receive might not be entirely detached. Was there not a case for having at least one representative of the senior registrars on this body? Mr. WALKER-SMITH said they could not interfere with the professional representation on this working party, which was a matter for the profession. He added that the composition of the working party was not yet decided. The Secretary of State for Scotland and himself would have to appoint their members, and he would bear in mind what Mr. Robinson had said.

Antenatal Radiography

Mr. B. JANNER (Leicester, North-west, Lab.) asked the Minister of Health if he could state the present policy of hospitals regarding *x*-ray examinations of expectant mothers, having regard to the potential danger to the unborn child.

Mr. WALKER-SMITH: It would be for the doctor concerned with any particular case to decide whether an expectant mother should be *x*-rayed, balancing his estimate of the potential danger against the medical value of the examination.

Smoking and Lung Cancer

Mr. W. HAMILTON (Fife, West, Lab.) asked what the Minister intended to do to intensify the publicity campaign showing the relationship between cigarette-smoking and lung cancer, in view of the recent report of the World Health Organization which showed an increase in recent years in the number of deaths from this disease.

Mr. RICHARD THOMPSON, Parliamentary Secretary, said the Minister would be obtaining further information on the campaigns which local health authorities had been undertaking during the 12-month period following the issue of the circular on this subject last June. He could not decide what further action might be necessary before studying the results. Mr. HAMILTON commented that there was considerable feeling in the country that the impact of the campaign had been nil.

Royal Assent.—The National Health Service Contributions Bill received the Royal Assent on April 30.

Health Visitors.—The Minister of Health is in general agreement with the recommendations of the working party on health visiting, and discussions on detail are proceeding with the local authority associations and professional organizations.

Vital Statistics

Doubtful Smallpox in Lincolnshire

A case of doubtful smallpox in a 30-year-old Arab steelworker has been reported at Scunthorpe, Lincs. The diagnosis had not been confirmed at the time of going to press, and clinically the disease was by then thought unlikely to be smallpox. The patient became ill on April 29, developed a rash on May 2, and was admitted to Laceby Hospital, near Grimsby, on May 4. He had apparently never been vaccinated. The usual precautions are being taken.

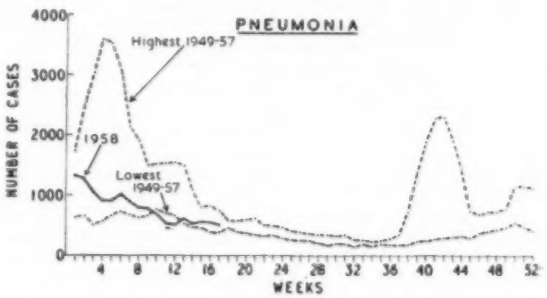
Industrial Accidents and Diseases

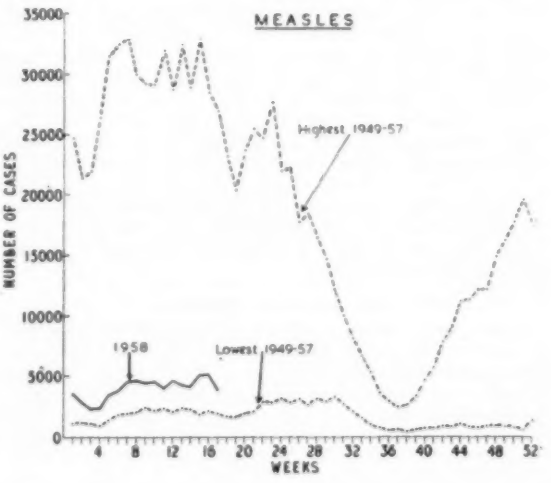
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in March was 124, compared with 122 in the previous month and 123 in March, 1957.

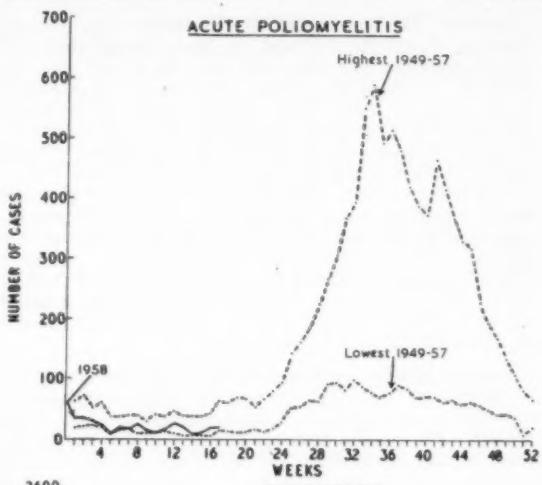
The numbers of cases of industrial diseases in the United Kingdom reported during March, 1958, were as follows: lead poisoning 6, compressed air illness 2, epitheliomatous ulceration 11, chrome ulceration 4; total 23. There was one death from epitheliomatous ulceration due to mineral oil.—*Ministry of Labour Gazette*, April, 1958.

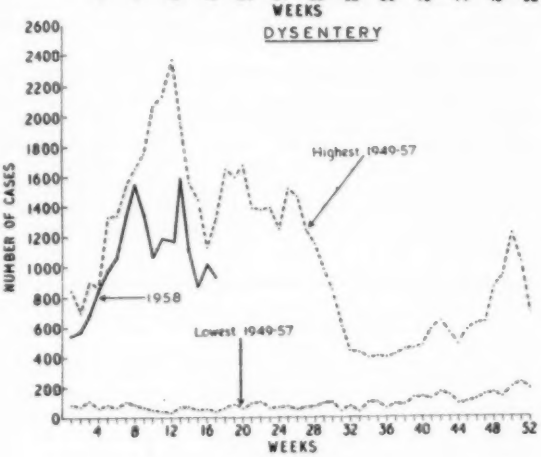
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending April 26

The largest falls in the notifications of infectious diseases in England and Wales during the week ending April 26 were 1,141 for measles, from 5,057 to 3,916, 83 for dysentery, from 1,010 to 927, 49 for acute pneumonia, from 556 to 507, and the largest rises were 116 for whooping-cough, from 539 to 655, and 29 for scarlet fever, from 599 to 628.

A decline in the incidence of measles was general throughout the country; the largest falls were 150 in London, from 444 to 294, 132 in Monmouthshire, from 189 to 57, 114 in Glamorganshire, from 229 to 115, and 105 in Leicestershire, from 268 to 163. Only small variations were recorded in the trends of the local returns of scarlet fever and whooping-cough. Three cases of diphtheria were notified during the week, being 2 more than in the preceding week.

The notifications of acute poliomyelitis numbered 21, and these were 2 fewer for paralytic and 4 more for non-paralytic cases than in the preceding week. The largest returns were Essex 3 (Southend-on-Sea C.B. 2) and Yorkshire West Riding 3.

The chief features of the returns of dysentery were falls of 70 in Yorkshire West Riding and 41 in Lancashire. The largest centres of infection during the week were Lancashire 235 (Manchester C.B. 45, Oldham C.B. 39, Liverpool C.B. 37, Chadderton U.D. 11, Crompton U.D. 11), Yorkshire West Riding 210 (Sheffield C.B. 27, Leeds C.B. 23, Dearne U.D. 18, Barnsley C.B. 16, Pontefract M.B. 14, Hemsworth R.D. 14, Bradford C.B. 11, Dewsbury C.B. 10, Huddersfield C.B. 10), London 78 (Islington 23), Gloucestershire 64 (Bristol C.B. 62), Staffordshire 48 (Kidsgrove U.D. 31), Surrey 44 (Godstone R.D. 16, Dorking and Horley R.D. 14), Durham 40, Nottinghamshire 36 (Nottingham C.B. 19, Worksop M.B. 12), and Cheshire 30 (Northwich R.D. 10).

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 19** (No. 16) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	1	0	4	0	1	7	0	0	0	1
Dysentery	1,010	95	171	12	6	874	36	235	21	6
Encephalitis, acute	5	0		0		4	0		1	
Enteric fever:										
Typhoid ..	3	1	0	0	2	4	0	0	0	2
Paratyphoid ..	4	2	0	0	4(B)	4	0	1(B)	0	
Food-poisoning ..	127	25	10	0		207	16	40	0	
Infective enteritis or diarrhoea under 2 years				9	29				22	15
Measles *	5,057	444	153	46	12	21,787	1767	257	363	220
Meningococcal infection	33	3	9	0	5	19	2	12	2	
Ophthalmia neonatorum	23	7	6	0		31	1	3	0	
Pneumonia † ..	556	41	269	13	5	382	29	171	4	13
Poliomyelitis, acute:										
Paralytic ..	15	2	2	3	3	26	16	3	1	5
Non-paralytic ..	4	0				4	0			
Puerperal fever § ..	173	27	13	3		193	33	5	0	
Scarlet fever ..	599	37	61	32	21	567	55	56	29	18
Tuberculosis:										
Respiratory ..	559	56	142	25		551	73	306	17	
Non-respiratory	62	4	21	5		60	7	8	5	
Whooping-cough ..	539	21	54	13	11	1,890	93	169	11	38

DEATHS	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	1	No comparable figures available.	0	0	0	0
Dysentery	0	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	1	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	0	0	2		0	0	1	0
Influenza	44	1	2	1	2		0	2	0	1
Measles		1	0	0	0		0	1	0	0
Meningococcal infection		0	0				1	0		
Pneumonia ..	696	54	34	13	10		22	13	3	5
Poliomyelitis, acute	5	1		1	0		1			1
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	130	9	11	0	2		7	4	2	8
Non-respiratory		2	2	0	2		2	0	0	0
Whooping-cough ..	0	0	0	0	0		0	0	0	0
Deaths 0-1 year ..	356	41	34	6	21		32	25	3	6
Deaths (excluding stillbirths) ..	11,465	878	708	136	235		769	559	110	138
LIVE BIRTHS ..	15,382	1273	1005	292	435		1032	826	204	345
STILLBIRTHS ..	361	34	26				19	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Rockefeller Foundation.—The grants announced by the Rockefeller Foundation for the first quarter of this year total over $4.28 million, of which $910,000 is for medical education and public health, and $576,000 for biological and medical research. One of the grants is a five-year grant of £10,000 and $5,000 to the Welsh Regional Hospital Board to support research on the biochemistry of the nervous system directed by Dr. DEREK RICHTER at Whitchurch Hospital, Cardiff. The Universities of Birmingham, Durham, Liverpool, and Sheffield receive grants ranging from $13,000 to $8,500 for scientific equipment, and Leeds University $7,000 to replace a radioactive cobalt source used for research.

Hospital Equipment Exhibition.—The MINISTER OF HEALTH opened the First International Hospital Equipment and Medical Services Exhibition at Olympia on Monday. The exhibition, which closes on Saturday, displays the products of 145 British manufacturers, and Mr. Walker-Smith described it as by far the largest exhibition in this field ever held. He said that the exhibition showed everything from beds and other furniture to catering and cleaning equipment, office equipment, and sterilization and therapeutic equipment. Supplies of the types shown, he added, cost about £20 million per annum in England and Wales. Among the more interesting exhibits are the new ultra-violet television microscope, which allows repeated photography of the living cell, and the prototype of a nerve stimulator energized by the operating theatre lights. Apart from the trade stands there is also an architectural section showing more than 50 current hospital building projects, including the new surgical blocks at Guy's and the new teaching hospital at Sheffield. In the historical section there is the Lister cabinet from the Royal College of Surgeons. During the exhibition the Institute of Hospital Administrators has been holding a series of lectures and discussions in the conference hall.

Association of the British Pharmaceutical Industry.—The annual dinner was held at the Savoy Hotel on April 30, with the president of the A.P.B.I., Dr. THOMAS KERFOOT, in the chair. Proposing the toast to the guests, Dr. Kerfoot said that it had been the constant aim of the pharmaceutical industry to put new tools into the hands of "our colleagues at the bedside, in the operating theatre, or in the laboratory." About 90% of the drugs in common use to-day were unknown twenty years ago. The industry was spending millions of pounds a year on research, and playing its part in keeping British medicine in its recognized place as among the finest in the world and among the cheapest. Speaking of the cost of drugs, Dr. Kerfoot said that investigation had shown that the price level of a fully representative sample of proprietary drugs not advertised to the public decreased between 1953 and 1957 by 18%. In reply, Mr. R. H. THOMPSON, Parliamentary Secretary to the Ministry of Health, said that the pharmaceutical industry had a fine story to tell, a story that should be more widely known. He referred to "the spectacular and praiseworthy efforts" made by the industry during the influenza epidemic: manufacturers coped with an enormous rush of orders and maintained an adequate supply of essential drugs during the crisis. A fine achievement of which the industry could be proud was the production of British-made freeze-dried B.C.G. vaccine. As to poliomyelitis vaccine, Mr. Thompson said that it was hoped that there would eventually be enough British vaccine to supply all Britain's needs. The Medical Research Council had always taken the view that the import of Salk vaccine should come to an end when British production was large enough. Mr. Thompson added: "In extolling our British vaccine I would like to express our appreciation to those Canadian and American organizations who are supplying a large part of our needs."

Scottish Midwives Board Reconstituted.—The Central Midwives Board for Scotland has been reconstituted. Of the 15 new members who will serve until 1963, five are medically qualified: Mr. J. BRUCE DEWAR, consultant obstetrician, Dumfries; Mr. DAVID MCKAY HART, gynaecologist, Glasgow; Dr. CATHERINE HARROWER, general practitioner, Glasgow; Professor R. A. LENNIE, regius professor of midwifery, Glasgow; and Dr. NORA WATTIE, medical officer, Glasgow Corporation. The full board consists of 16 members. Seven are practising midwives, of whom three are appointed by the Secretary of State for Scotland, and four are elected by certified midwives practising in Scotland. The remaining nine members are representative of medical bodies, local authorities, the universities, and the hospital services. The board supervises the training and professional discipline of midwives in Scotland.

Foreign Member of Royal Society.—Dr. ANDRÉ LWOFF, of the Pasteur Institute, Paris, was one of four distinguished scientists recently elected to foreign membership of the Royal Society. The citation describes him as distinguished for his work on the morphology and nutritional requirements of protozoa, and for his researches on lysogenic bacteria and bacteriophage.

Whitby Memorial Fund.—The council of the Senate of Cambridge University propose to establish a Sir Lionel Whitby memorial fund. The £3,500 given to the University last year in memory of Sir Lionel Whitby by American Service men and civilians in Britain, on the recommendation of the 7,510th U.S. Air Force Hospital, Wimpole Park, will be used to establish the fund, and its income will be placed at the disposal of the head of the university department of pathology.

Upjohn Travelling Fellowships.—Applications are invited from members of the College of General Practitioners for not less than 15 travelling fellowships of up to £200 each in value. These fellowships are to enable general practitioners to carry out a minimum of two weeks' postgraduate study at their old teaching hospitals or at any other hospital, clinic, health centre, or general practice of their choice. Further details and application forms may be obtained from the College of General Practitioners, 41, Cadogan Gardens, London, S.W.3. Applications should be returned before September 1. The names of the successful candidates will be announced at the College's annual meeting on November 22.

Simpson-Smith Memorial Prize.—The Institute of Child Health is offering a Simpson-Smith memorial prize for 1959 for the best dissertation or essay on "Spina Bifida." The prize is open to men and women from the British Commonwealth or the Republic of Ireland who are engaged in the practice of surgery. The prize will consist of a money award of 100 guineas. A copy of the rules can be obtained from the secretary, Institute of Child Health, the Hospital for Sick Children, Great Ormond Street, London, W.C.1.

Birmingham University.—Dame HILDA ROSE (formerly Dame Hilda Lloyd), president of the Royal College of Obstetricians and Gynaecologists from 1949 to 1952 and emeritus professor of obstetrics and gynaecology at Birmingham, is to receive the University's honorary LL.D. on July 5, and Professor A. M. B. LACASSAGNE, director of the Radium Institute at the Pasteur Institute, Paris, the honorary D.Sc. Dr. G. H. THOMAS, Ph.D., has been appointed senior lecturer in endocrine chemistry in the department of anatomy.

Picture in R.A. Exhibition.—Dr. P. TUTTNAUER has had his picture, *Boats at Rest*, hung in the Royal Academy's summer exhibition.

Professor Jethro Gough, professor of pathology in the Welsh National School of Medicine, lectured at the Mayo Clinic on April 21 on "Some Recent Investigations in Pulmonary Pathology."

COMING EVENTS

National Marriage Guidance Council.—Annual conference, May 15–18 at Hastings. Details from the council, 78, Duke Street, Grosvenor Square, London, W.1.

Fever Hospital Medical Services Group.—Meeting at the Royal Free Hospital (North-western Branch), Lawn Road, London, N.W.3, May 16 and 17, at 10 a.m. Details from the hon. secretary, Neasden Hospital, London, N.W.10.

Indian Medical Service Dinner Club.—Annual dinner, June 13, at the East India and Sports Club, 7 for 7.30 p.m. Tickets from the secretary of the club, Medical Board Room, Commonwealth Relations Office, Matthew Parker Street, London, S.W.1.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The Journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Industrial Medicine.—Issued quarterly (£3 annually). The new issue, Vol. 15, No. 2, includes :

RESPIRATORY FUNCTION DURING THE DAY IN COTTON WORKERS: A STUDY IN BYSSINOSIS. C. B. McKerrow, M. McDermot, J. C. Gilson, and R. S. F. Schilling.

A HISTOLOGICAL STUDY OF THE LUNGS IN 52 CASES OF CHRONIC BERYLLIUM DISEASE. W. Jones Williams.

THE EFFECT OF DIAMOND DUST ALONE AND MIXED WITH QUARTZ ON THE LUNGS OF RATS. E. J. King, M. Yoganathan, and G. Nagelschmidt.

THE PREVALENCE OF PULMONARY TUBERCULOSIS IN A NORTHERN TRANSVAAL COPPER-MINE RELATED TO THE IMPORTANCE OF PRE-EMPLOYMENT RADIOGRAPHS. G. E. Dalton.

SOME PRELIMINARY THOUGHTS ON THE HUMAN DEMANDS OF AUTOMATION. A. T. Welford.

A CLINICAL STUDY OF BEAT KNEE. J. T. Watkins, T. A. Hunt, R. H. P. Fernandez, and O. P. Edmonds

THE PARADOX IN THE TREATMENT OF BEAT KNEE. R. H. P. Fernandez.

THE SEDIMENTATION RATE AND FRAGILITY OF HUMAN ERYTHROCYTES IN VITRO AFTER EXPOSURE TO LEAD CHLORIDE. T. W. Clarkson and J. E. Kench.

THE EFFECTS OF BURSTS OF LOUD NOISE ON A CONTINUOUS VISUAL TASK. M. M. Woodhead.

A METHOD FOR THE DETERMINATION OF TRINITROTOLUENE IN AIR. J. Mackay, K. W. Holmes, and R. E. Wilson.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 12

DONCASTER MEDICAL SOCIETY.—At Newton Hotel, Sprotborough Road, 8 p.m., annual general meeting.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—6 p.m., Dr. Joel Pressman (Los Angeles): Clinical Anatomy of the Larynx in Relation to the Spread of Cancer.

PLYMOUTH MEDICAL SOCIETY.—At Greenbank Road Hospital, 8.30 p.m., annual general meeting.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Depressive Illness (II).

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. B. A. Stone: Biochemistry of Cellulose and Related Polysaccharides.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., Almroth Wright Lecture by Professor J. R. Squire: Hypogammaglobulinaemia: Clinical and Laboratory Studies on the Gamma Globulins.

Tuesday, May 13

BIRMINGHAM UNIVERSITY: FACULTY OF MEDICINE.—At Large Anatomy Theatre, Medical School, 4 p.m., William Withering Lecture by Professor J. S. Mitchell, F.R.S.: Studies in Radiotherapeutics.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. G. Cochrane: Leprosy (1).

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 2 p.m., Professor W. C. W. Nixon: An Integrated Obstetric Service.

LONDON UNIVERSITY.—At Physiology Lecture Theatre, St. Bartholomew's Hospital Medical College, E.C., 5 p.m., special university lecture in medicine by Professor H. Rocke Robertson (British Columbia): Venous Thrombosis.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Croonian Lecture by Dr. Paul H. Wood: Eisenmenger Syndrome, or Pulmonary Hypertension with Reversed Central Shunt.

Wednesday, May 14

BIRMINGHAM UNIVERSITY: FACULTY OF MEDICINE.—At Large Anatomy Theatre, Medical School, 4 p.m., William Withering Lecture by Professor J. S. Mitchell, F.R.S.: Studies in Radiotherapeutics.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. G. Cochrane: Leprosy (2).

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Lynne Reid: Mucus Secretion in Normal and Morbid Lung.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. I. R. H. Kramer: Giant Cell Diseases of the Oral Cavity.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor Jan Waldenstrom: Carcinoidosis and Some Allied Conditions.

Thursday, May 15

BIRMINGHAM UNIVERSITY: FACULTY OF MEDICINE.—At Large Anatomy Theatre, Medical School, 4 p.m., William Withering Lecture by Professor J. S. Mitchell, F.R.S.: Studies in Radiotherapeutics.

BRITISH INSTITUTE OF RADIOLOGY.—7.30 p.m., annual general meeting, 8 p.m., Silvanus Thompson Memorial Lecture by Professor F. S. Dainton, Sc.D., F.R.I.C., F.R.S.: Radiation Chemistry in Retrospect and in Prospect.

COLLEGE OF GENERAL PRACTITIONERS: NORTH-WEST ENGLAND FACULTY.—At Clinical Sciences Building, Manchester University, 9 p.m., Second Annual Pfizer Lecture by Dr. E. M. Bluestone (New York): Unsolved Problems in Organized Medical Care.

HYPNOTHERAPY GROUP.—At Royal Society of Medicine, 8 p.m., discussion: Anxiety. Speakers, Dr. D. Stafford-Clark, Dr. T. A. Kemp, and Dr. W. Moodie.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, 8.30 p.m., Mr. I. S. Smillie: Loose Bodies in Joints.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor G. M. Wilson: Simple and Malignant Goitre.

ROYAL ANTHROPOLOGICAL INSTITUTE OF GREAT BRITAIN AND IRELAND.—5.30 p.m., Dr. Raymond Cabannes (Algiers): Distribution of Abnormal Haemoglobins in Algeria, Hoggar, and High Volta.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Croonian Lecture by Dr. Paul H. Wood: Eisenmenger Syndrome, or Pulmonary Hypertension with Reversed Central Shunt.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., Dr. J. R. Audy: Localization of Disease, with special reference to the Zoonoses. A discussion will follow.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Wellcome Foundation, Euston Road, N.W., 6.30 p.m., demonstration at Wellcome Historical Medical Museum and Harvey Tercentenary Exhibition, followed by cocktail party.

Friday, May 16

COLLEGE OF GENERAL PRACTITIONERS: YORKSHIRE FACULTY.—At Littlewood Hall, General Infirmary at Leeds, 8.30 p.m., Pfizer Lecture by Dr. Rex Tattersall: Recent Advances in Therapeutics.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4.45 p.m., Second Knox Memorial Lecture by Professor D. W. Smithers: Tumours of the Thyroid in Relation to Some General Concepts of Neoplasia.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. F. R. Bettley: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. G. Scadding: clinical demonstration.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Miss D. M. Shotton: Pelvic Tuberculosis.

LEICESTER CHRISTIAN MEDICAL ASSOCIATION.—At Leicester Royal Infirmary, 8.30 for 8.45 p.m., Rev. Brian Hession: Cancer Anonymous.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, W.C., 5.30 p.m., special university lecture in pathology by Dr. Ludwick Gross (New York): Viral Aetiology of Mouse Leukaemia—its Possible Implications for the Problem of Cancer.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. I. S. R. Sinclair: Surgical Aspects of Pancreatic Disease.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Dr. R. R. Willcox: Gonorrhoea in Gynaecological Practice.

Saturday, May 17

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, University of Edinburgh, 11.30 a.m., meeting.

YORKSHIRE SOCIETY OF ANAESTHETISTS.—At Hull Royal Infirmary, 10 a.m., lecture demonstrations arranged by Dr. W. N. Rollason. Dr. J. D. Robertson: Anaesthesia Made Difficult.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Honey.—On April 27, 1958, at University College Hospital, London, W.C., to Drs. Joyce and Michael Honey, a daughter—Ruth Mary.

Millington.—On April 25, 1958, at Widnes Maternity Hospital, Widnes, Lancs, to Mavis, wife of Dr. Douglas Millington, a sister for Rachel and Robert—Claire.

DEATHS

Adam.—On April 10, 1958, George Henry Adam, M.R.C.S., L.R.C.P., of Malling Place, West Malling, Kent.

Brown.—On April 17, 1958, at 51, Minto Street, Edinburgh, Andrew Johnstone Brown, T.D., F.R.C.S.Ed., L.D.S.

Burman.—On April 17, 1958, in Grey's Hospital, Pietermaritzburg, South Africa, Charles Ernest Lewis Burman, M.B., B.S., formerly of Alnwick, Northumberland.

Christie.—On May 3, 1958, in hospital, James Souter Christie, M.B., C.M., J.P., of Hove, Eaglesfield, by Lockerbie, Dumfriesshire.

Cowan.—On April 16, 1958, at the Fazakerley Hospital, Liverpool, Charles Robert Cowan, M.B., B.S., of Ellesmere Port, Cheshire, late of Ossett, Yorks, aged 32.

Davidson.—On April 17, 1958, at Kelso Cottage Hospital, Samuel Davidson, M.D., J.P., of Kildonan, Yetholm, Kelso, Roxburghshire, aged 86.

Howard.—On April 16, 1958, in a nursing-home, Jersey, Stewart Carlisle Howard, M.D., late of Malaya.

Iliffe.—On April 14, 1958, at Derby Royal Infirmary, Caris William Iliffe, L.R.C.P.&S.Ed., L.R.F.P.S., of 76, Belper Road, Derby, aged 87.

Lacey.—On April 11, 1958, at Langton Farm, Balcombe, Sussex, Frank Hamilton Lacey, T.D., M.D., F.R.C.O.G.

Lowe.—On April 12, 1958, in a nursing-home, Southport, Lancs, Edward Cronin Lowe, M.B.E., M.B., B.S., F.R.I.P.H.H., aged 77.

Sequeira.—On April 11, 1958, Walter Scott Harcourt Sequeira, M.B., Surgeon Captain, R.N., retired, of Northover, Ilchester, Somerset, aged 88.

Soden.—On April 21, 1958, Thomas Armand Bourne Soden, M.R.C.S., J.P., of Leamington Spa, and Coventry, Warwicks, aged 98.

Whitlow.—On April 6, 1958, at his home, Bethersden, Kent, Arthur Robert Newing Whitlow, M.B., B.S.

Young.—On April 17, 1958, at his home, 9 Hastings Place, Lytham, Lancs, John Stirling Young, M.D.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Testicular Hormone in Corticotherapy

Q.—*Is it justifiable to administer testicular hormone during corticotherapy as an anabolic counter to the protein catabolic effect of corticosteroids and to combat osteoporosis?*

A.—The use of testosterone in combating osteoporosis is theoretically desirable, but it cannot be administered in sufficient dosage without undesirable androgenic effects, especially in female patients. Several synthetic substances have been developed—for example, 17α-ethyl-19-nortestosterone and androstenediol—which have the desirable anabolic properties with respect to protein and calcium with less androgenic effect than testosterone. Nevertheless, in useful dosage some androgenic effect is evident. The use of an oestrogen, such as stilboestrol or ethinyl oestradiol, should be considered as an adjunct to the treatment in a post-menopausal woman. None of these supplementary measures should be used as a routine, but only in special circumstances after careful appraisal of all the relevant factors in a particular patient. This usually means answering the question: Is the nature and severity of the disease worth the risk of high dosage therapy? Extra care is obviously necessary when the more complex methods of management are still thought to be desirable, and the patient should be seen frequently and the necessary adjustments of dosage made.

Bathing after Meals

Q.—*It is said to be unwise to bathe until at least an hour has elapsed since a meal. Is this correct and, if so, what is the physiological reason?*

A.—This old warning still persists, but it is evidently often neglected, and most children (and many adults) bathe immediately after a meal without any obvious ill effects. If it had any physiological basis, it probably lay in the following beliefs: (1) that the full stomach dragged on the diaphragm and impeded respiration; (2) that the peripheral musculature was relatively anoxic and, hence, liable to cramps, the bulk of the blood having been centred in the mesenteric area for digestive purposes; (3) that blood coagulability showed a post-prandial rise. Surely not very convincing theories.

Sedimentation Rate in Paget's Disease

Q.—*Is the sedimentation rate raised in uncomplicated Paget's disease?*

A.—The sedimentation rate appears to be raised in a number of cases of active Paget's disease, and is usually normal in patients in whom the disease is quiescent. However, Paget's disease of bone occurs in an age group where there are often multiple pathological lesions, and it is always difficult to say a patient has only one disease. Recent published studies of this include Grainger and Laws,[1] and Rosenkrantz *et al.*[2] There appears to be little correlation with the extent of the bone change.

REFERENCES

[1] Grainger, R. G., and Laws, J. W., *Brit. J. Radiol.*, 1957, **30**, 120.
[2] Rosenkrantz, J. A., Wolf, J., and Kaicher, J. J., *Arch. intern. Med.*, 1952, **90**, 610.

Susceptibility to Sunburn

Q.—*What can be done to protect a patient who is very susceptible to sunburn?*

A.—Acquired light sensitivity may be a symptom of general disorder, particularly porphyria, systemic lupus erythematosus, and perhaps vitamin deficiency and certain drug sensitivities. For this reason a patient such as the one quoted should be investigated for any possible underlying disorder. If no abnormality is found, protection from the sun may be achieved in a variety of ways.

First, it may be possible gradually to acquire light tolerance again by progressive treatment with a carbon-arc lamp. A second method is by the administration of drugs of the antimalarial group which diminish light sensitivity during the time of their administration. Of these drugs the most satisfactory at present seems to be chloroquine, which may be given in divided doses up to 400 or 500 mg. daily. Some prefer to give a combination of chloroquine, "plaquenil" (hydroxychloroquine sulphate), and mepacrine with the object of achieving the same therapeutic effect with fewer side-effects. Thirdly, the skin may be protected with local applications. Many of these are on the market and most of them are satisfactory and harmless. The usual substances prescribed are creams or lotions containing 10% of tannic acid or 5 to 10% *para*-aminobenzoic acid. The protection of the skin from light by local applications has been well reviewed by R. G. Harry.[1]

REFERENCE

[1] Harry, R. G., *Modern Cosmeticology*, 1955. Leonard Hill, London.

Intra-arterial Blood Transfusion

Q.—*What are the common indications for and the technique and dangers of intra-arterial blood transfusion?*

A.—There are very few indications for intra-arterial transfusion; indeed, some would say there are none. It has been claimed that in subjects exsanguinated to the point of death intra-arterial transfusion would save life when intravenous transfusion would not, and that the advantage may lie in the fact that the coronary circulation is filled directly when blood is introduced into the arterial side of the circulation. From experimental work it seems clear that profound exsanguination alone is not an indication for intra-arterial transfusion. In dogs bled to hypotensive levels, coronary flow and arterial pressure respond equally rapidly whether blood is given intravenously or intra-arterially.[1] It seems that the arterial route should be considered only when the heart is arrested or when, as during cardiac surgery, the circulation has been interfered with. Unless the systolic pressure is very low, considerable pressure will be required to force blood rapidly into the artery. Some form of rotary pump is the best equipment for the purpose. The main complications of intra-arterial transfusion are, first, embolism, and, secondly, when an artery in a limb is used, gangrene of the extremity.

REFERENCE

[1] Case, R. B., Sarnoff, S. J., Waithe, P. E., and Sarnoff, L. C., *J. Amer. med. Ass.*, 1953, **152**, 208.

Correction.—Dr. PETER DELLER (London, S.W.1) writes: "In my letter of last week (*Journal*, May 3, p. 1067) I referred by a slip of the pen to 'the late' Mr. T. B. Layton. Mr. Layton is, of course, very much alive, and I tender him humble apologies for a gross exaggeration." We should like to add our apologies to Dr. Deller's, for not noticing this mistake.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

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Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d.).
Clinical Pathology in General Practice (22s. 3d.).
Any Questions?, Volumes 2 and 3 (8s. 3d. each).

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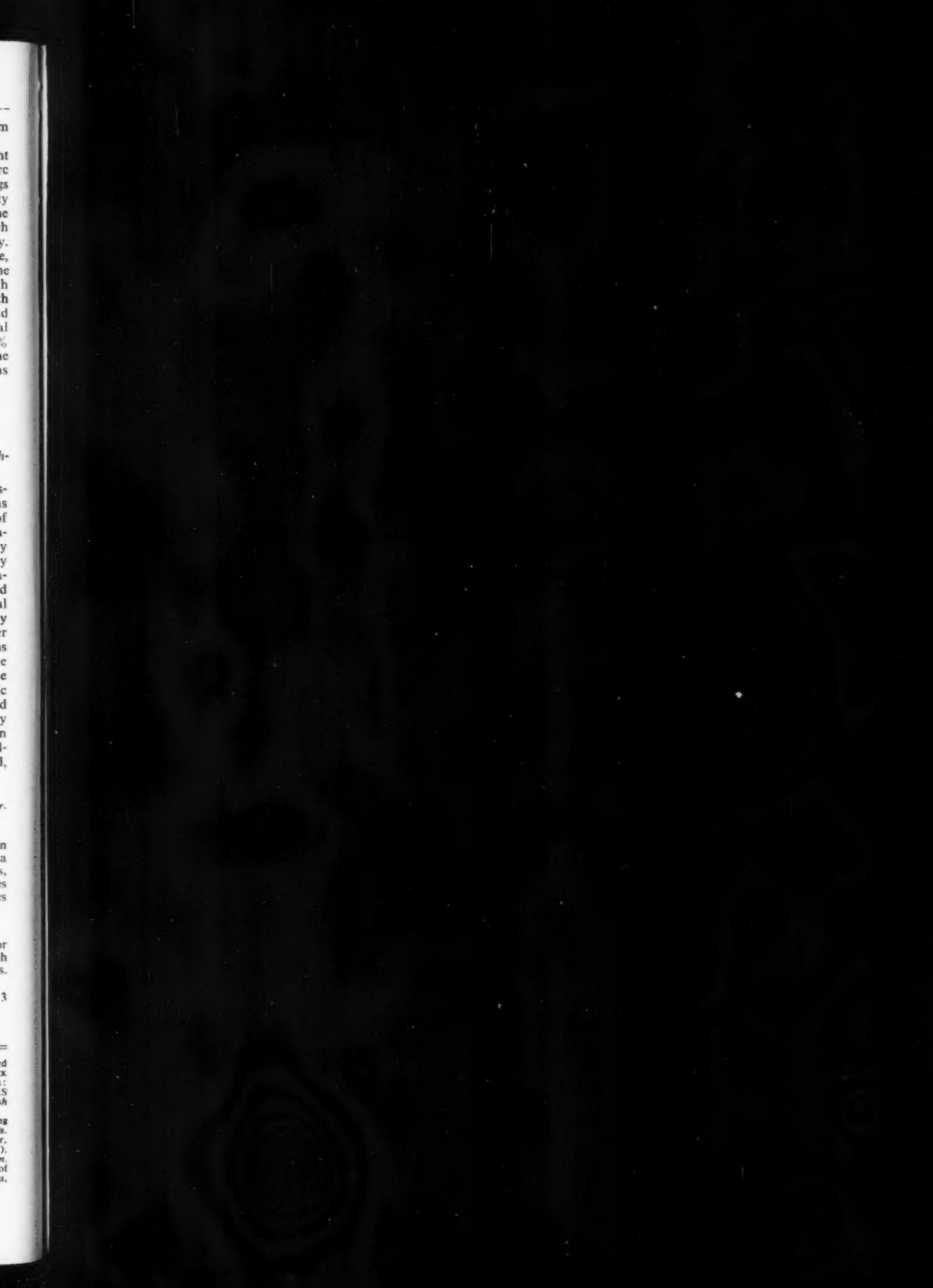
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